Immunogenicity and safety of a cell culture-derived inactivated quadrivalent influenza vaccine (NBP607-QIV) in South Korean children and adolescents : A randomized, double-blind, multi-center, phase 3 clinical trial

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Abstract

- **Background.** Cell culture-derived influenza vaccines have several important advantages over egg-based influenza vaccines and inactivated quadrivalent influenza vaccine (IIV4) may offer broader protection against seasonal influenza than inactivated trivalent influenza vaccine (IIV3) by containing one more B strain. This study examined the immunogenicity and safety of a cell culture-derived IIV4 candidate vaccine in children and adolescents.
- **Methods.** This phase III, randomized, double-blind, multicenter trial in children/adolescents (6 month through 18 years) was conducted in South Korea. Children/adolescents were randomized 4:1 to receive one of novel cell culture-derived, subunit, IIV4 (NBP607-QIV, SK Chemicals, Seongnam, Korea) or licensed IIV3 (Agrippal®S1, Novartis Vaccines and Diagnostics Srl, Siena, Italy). Haemagglutination inhibition antibody titers were assessed pre-vaccination and 28 days post-vaccination. Safety data were collected for up to 6 months post-vaccination.
- **Results.** 366 children/adolescents received IIV4, and 88 children/adolescents received IIV3. Overall, NBP607-QIV met the immunogenicity criteria of Committee for Medicinal Products for Human Use for each of the 4 strains. Between the NBP607-QIV and control groups, immunogenicity endpoints were comparable. Participants younger than 3 years of age had lower immunologic responses against 2 influenza B strains in both NBP607-QIV and control group. No deaths, vaccine-related SAEs, or withdrawals because of adverse events were reported. The solicited adverse events reported were generally of mild intensity.
- **Conclusions.** NBP607-QIV, a novel cell culture-derived IIV4, showed good immunogenicity to all 4 influenza strains and had tolerable safety profiles in children and adolescents. Moreover, NBP607-QIV was more immunogenic against influenza B compared to the control, an egg-based subunit vaccine.

Backgrounds

- For years, influenza vaccines were designed to protect against three different flu viruses, which included an influenza A H1N1 virus, an influenza A H3N2 virus and one B virus.
- However, influenza B strains have diverged into two lineages, known as Victoria and Yamagata.
- The two lineages are antigenically distinct and it is difficult to expect cross-protection between the lineages.
- Actually, the mismatch between circulating influenza B viruses and vaccine strains has been occurred frequently and the B lineage selected for seasonal vaccines has matched the dominant circulating strain only about half the time..
- To address this mismatch, the WHO has recommended a fourth strain to be included in seasonal influenza vaccines since 2012.
- Cell-culture influenza vaccines are being developed as an alternative to the egg-based manufacturing process because the technology is more flexible than the traditional technology, which relies upon adequate supply of eggs.
- The main benefit of the cell-culture system is the ability to rapidly produce vaccine supplies during an impending pandemic and the avoidance of egg-related allergic reactions.
- SK Chemicals has developed cell culture-derived quadrivalent inactivated influenza vaccine (NBP607-QIV) first in the world.
- We investigated the immunogenicity and safety of cell culture-derived quadrivalent inactivated influenza vaccine in children and adolescents subjects

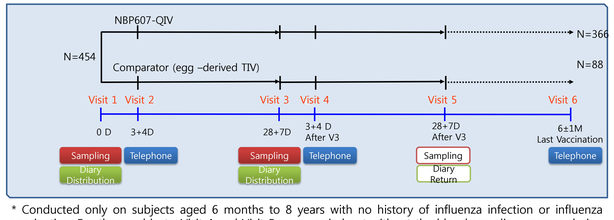
Methods

- **Study design**: a randomized controlled phase III trial
- **Study subjects**
  - South Korean children and adolescents subjects (aged from 6months to 18 years)
  - Assignment of subjects randomly in a 4:1 ratio to NBP607-QIV versus egg-derived TIV (B-Yamagata)
- **Total number of study subjects** : Total 454 subjects

Age	NBP607-QIV group	Comparator group	Total
6 months – 2 years old	111 subjects	25 subjects	136 subjects
3 – 8 years old	128 subjects	31 subjects	159 subjects
9 – 18 years old	127 subjects	32 subjects	159 subjects

- **NBP607-QIV** : cell(MDCK) culture derived quadrivalent subunit inactivated influenza vaccine (SKYCellflu, SK Chemicals, Andong, Korea)
- **Comparator** : licensed egg-derived trivalent subunit inactivated influenza vaccine (Agrippal®S1, Novartis Vaccines and Diagnostics Srl, Siena, Italy).
- **Study sites**: 9 university hospitals in Republic of Korea

- **Immunogenicity** : To assess Immunogenicity 4weeks after vaccination by haemagglutination inhibition assay.
- **Safety** : To assess solicited adverse events (AEs) for 7 days, unsolicited AEs for 28 days and serious adverse events (SAEs) for 6 months.
- **Study period**: September 2014 – June 2015
- **Primary outcome**
  - Immunogenicity assessment using CHMP criteria in the children and adolescents subject at Day 28 post vaccination
    : Seroprotection rate >70% ; Seroconversion rate >40% ; GMR >2.5
- **Secondary outcome**
  - Assessment of immunogenicity in subjects with pre-vaccination titer <1:80
  - Comparison of immunogenicity parameters between the test group and the comparator group
- **ClinicalTrials.gov Identifier**: NCT02621164

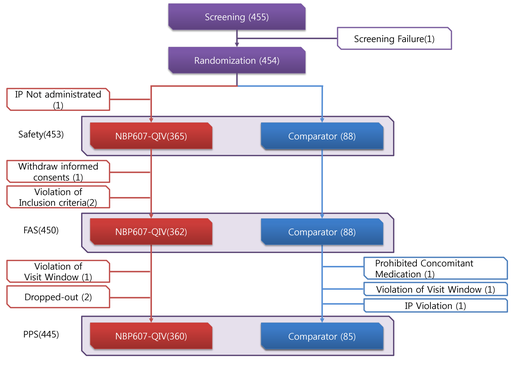


* Conducted only on subjects aged 6 months to 8 years with no history of influenza infection or influenza vaccination. For these subjects, Visit 4 and Visit 5 were carried out without the blood sampling process during Visit 3.

* In accordance with the safety data monitoring guideline, 30 subjects were initially vaccinated with NBP607-QIV or Comparator and their safety information were collected up until visit 2 (7+3D). The enrollments of rest of subjects were initiated only after it was found that no SADR was identified from the safety data of 30 subjects.

Results

- **Subject disposition (total no=454)**



- **Baseline characteristics**

	N	NBP607-QIV 366	Comparator 88	Total 454	P-value
Gender	Male	193(52.73)	42(47.73)	235(51.76)	0.3989[1)]
	Female	173(47.27)	46(52.27)	219(48.24)	
Age	Mean±SD (months)	82.75±58.88	86.13±60.63	83.40±59.17	0.6557[2)]
	Median (months)	71.00	78.00	71.50	
	Min–Max (months)	7.00–224.00	6.00–227.00	6.00–227.00	
	6 months≤ Age <3 years	111(30.33)	25(28.41)	136(29.96)	0.9302[1)]
	3 years ≤ Age <9 years	128(34.97)	31(35.23)	159(35.02)	
	9 years ≤ Age ≤18 years	127(34.70)	32(36.36)	159(35.02)	
Vaccination Dose	2 dose	53(14.48)	7(7.95)	60(13.22)	0.1046[1)]
	1 dose	313(85.52)	81(92.05)	394(86.78)	
Influenza Vaccination of previous year	Yes	251(68.58)	62(70.45)	313(68.94)	0.7328[1)]
	No	115(31.42)	26(29.55)	141(31.06)	

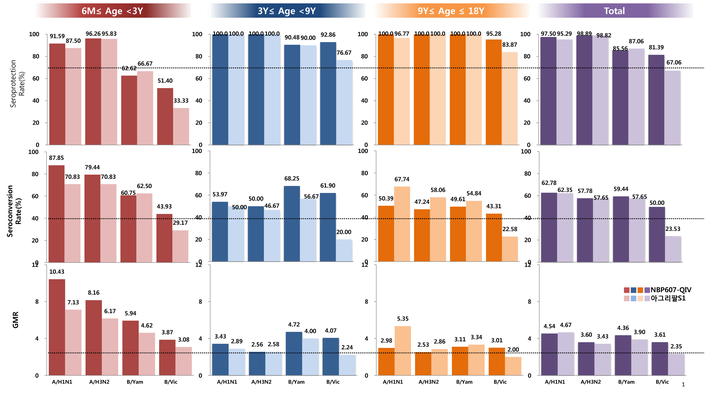
[1)] Chi-square test
[2)] Wilcoxon rank sum test

- **Immunogenicity**

For the four influenza strains(A/H1N1, A/H3N2, B/Yamagata, B/Victoria) post-vaccination serologic data in NBP607 QIV group met the all CHMP criteria

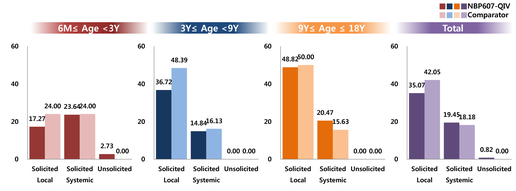
Strain		6 months≤ Age <3 years NBP607-QIV (N=107)	Comparator (N=24)	P-value	3 years ≤ Age <9 years NBP607-QIV (N=360)	Comparator (N=85)	P-value	9 years ≤ Age ≤ 18 years NBP607-QIV (N=127)	Comparator (N=31)	P-value	Total NBP607-QIV (N=360)	Comparator (N=85)	P-value
A/H1N1	SPR, N(%)	98(91.59)	21(87.50)	0.4599††	126(100.00)	30(100.00)	-	127(100.00)	30(96.77)	0.1962†	351(97.50)	81(95.29)	0.2841††
	SCR, N(%)	94(87.85)	17(70.83)	0.0555††	68(53.97)	15(50.00)	0.6954†	64(50.39)	21(67.74)	0.0824†	226(62.78)	53(62.35)	0.9419†
	Pre-GMT	17.68±4.13	22.45±4.04	0.4564‡	179.59±3.58	192.48±2.71	0.7815‡	209.06±2.85	119.64±3.81	0.0131‡	95.14±5.25	88.22±4.56	0.7018‡
	Post-GMT	184.51±3.96	160.00±4.12	0.6490‡	615.82±2.37	557.15±2.09	0.5593‡	622.77±2.06	640.00±3.01	0.8965‡	432.11±3.14	412.04±3.45	0.7345‡
	GMR	10.43±3.32	7.13±3.10	0.1577‡	3.43±2.50	2.89±2.15	0.3495‡	2.98±2.50	5.35±3.18	0.0030‡	4.54±3.14	4.67±2.95	0.8384‡
A/H3N2	SPR, N(%)	103(96.26)	23(95.83)	1.0000††	126(100.00)	30(100.00)	-	127(100.00)	31(100.00)	-	356(98.89)	84(98.82)	1.0000††
	SCR, N(%)	85(79.44)	17(70.83)	0.3587†	63(50.00)	14(46.67)	0.7428†	60(47.24)	18(58.06)	0.2800†	208(57.78)	49(57.65)	0.9825†
	Pre-GMT	30.28±6.36	37.75±4.99	0.5901‡	306.22±3.20	350.98±2.29	0.4598‡	267.26±2.99	279.82±3.38	0.8380‡	146.72±5.59	172.18±4.71	0.4327‡
	Post-GMT	246.95±3.90	232.90±4.12	0.8503‡	784.47±2.28	905.10±1.82	0.2806‡	675.90±2.22	800.36±2.51	0.3069‡	527.91±3.07	589.88±3.16	0.4141‡
	GMR	8.16±3.18	6.17±2.88	0.2797‡	2.56±2.17	2.58±1.85	0.9655‡	2.53±2.27	2.86±2.22	0.4527‡	3.60±2.89	3.43±2.45	0.6936‡
B/Yamagata	SPR, N(%)	67(62.62)	16(66.67)	0.7098†	114(90.48)	27(90.00)	1.0000††	127(100.00)	31(100.00)	-	308(85.56)	74(87.06)	0.7207†
	SCR, N(%)	65(60.75)	15(62.50)	0.8736†	86(68.25)	17(56.67)	0.2285†	63(49.61)	17(54.84)	0.6014†	214(59.44)	49(57.65)	0.7618†
	Pre-GMT	7.05±1.89	6.87±1.78	0.8560‡	21.72±3.09	20.47±3.09	0.7959‡	64.66±2.71	59.82±2.74	0.6982‡	22.84±3.69	22.24±3.62	0.8644‡
	Post-GMT	41.86±3.53	31.75±2.76	0.3179‡	102.47±2.59	81.87±2.60	0.2471‡	201.22±2.08	200.09±1.92	0.9688‡	99.64±3.22	86.80±3.12	0.3265‡
	GMR	5.94±2.91	4.62±2.89	0.3004‡	4.72±2.31	4.00±2.16	0.3271‡	3.11±2.28	3.34±2.58	0.6713‡	4.36±2.57	3.90±2.52	0.3274‡
B/Victoria	SPR, N(%)	55(51.40)	8(33.33)	0.1093†	117(92.86)	23(76.67)	0.0159††	121(95.28)	26(83.87)	0.0408††	293(81.39)	57(67.06)	0.0037†
	SCR, N(%)	47(43.93)	7(29.17)	0.1843†	78(61.90)	6(20.00)	<0.0001†	55(43.31)	7(22.58)	0.0341†	180(50.00)	20(23.53)	<0.0001†
	Pre-GMT	7.47±2.22	6.67±2.08	0.5262‡	28.28±3.19	25.20±3.73	0.6335‡	51.14±2.75	43.74±3.09	0.4529‡	23.47±3.59	21.17±3.81	0.5091‡
	Post-GMT	28.93±3.60	20.59±3.09	0.2324‡	115.02±2.70	56.57±3.15	0.0008‡	154.00±2.51	87.48±2.78	0.0032‡	84.59±3.59	49.85±3.44	0.0006‡
	GMR	3.87±3.09	3.08±2.54	0.3596‡	4.07±2.50	2.24±2.17	0.0013‡	3.01±2.29	2.00±2.32	0.0151‡	3.61±2.62	2.35±2.35	0.0002‡

Difference between treatment groups(† chi-square test †† Fisher's exact test‡ two sample t-test)



- **Safety**

- Adverse event (AE)



- Solicited Adverse Drug Reaction (ADR)

Solicited ADR	6 months ≤ Age < 3 years NBP607 QIV	Compa rator	P-value†	3 years ≤ Age < 9 years NBP607 QIV	Compa rator	p-value	9 years ≤ Age < 12 years NBP607 QIV	Compa rator	p-value	12 years ≤ Age ≤ 18 years NBP607 QIV	Compa rator	p-value
N	110	25		128	31		58	17		69	15	
Solicited Local	19(17.27)	6(24.00)	0.4077	47(36.72)	15(48.39)	0.2320	32(55.17)	10(58.82)	0.7897†	30(43.48)	6(40.00)	0.8051†
Pain	13(11.82)	6(24.00)	0.1216	32(25.00)	12(38.71)	0.1258	24(41.38)	10(58.82)	0.2039†	22(31.88)	3(20.00)	0.5356††
Redness	7(6.36)	3(12.00)	0.3931	27(21.09)	8(25.81)	0.5699	21(36.21)	1(5.88)	0.0161††	2(2.90)	0(0.00)	1.0000††
Swelling	6(5.45)	1(4.00)	1.0000	19(14.84)	7(22.58)	0.2960	10(17.24)	1(5.88)	0.4382††	0(0.00)	0(0.00)	-
Tenderness	-	-	-	-	-	-	-	-	-	26(37.68)	5(33.33)	0.7518†
Solicited Systemic	26(23.64)	6(24.00)	0.9692†	19(14.84)	5(16.13)	0.7867	16(27.59)	3(17.65)	0.5343	10(14.49)	2(13.33)	1.0000
Myalgia	4(3.64)	0(0.00)	1.0000††	11(8.59)	1(3.23)	0.4632	11(18.97)	2(11.76)	0.7197	7(10.14)	1(6.67)	1.0000
Irritability	22(20.00)	5(20.00)	1.0000†	6(4.69)	2(6.45)	0.6541	1(1.72)	0(0.00)	1.0000	-	-	-
Sleepiness	14(12.73)	4(16.00)	0.7445††	6(4.69)	2(6.45)	0.6541	3(5.17)	1(5.88)	1.0000	-	-	-
Fatigue	-	-	-	6(7.59)	2(10.53)	-	5(8.62)	1(5.88)	0.6500	5 1.0000	2(13.33)	0.6030
Headache	1(0.91)	0(0.00)	1.0000††	4(3.13)	1(3.23)	1.0000	6(10.34)	2(11.76)	1.0000	4(5.80)	1(6.67)	1.0000
Fever	3(2.73)	1(4.00)	0.5637††	1(0.78)	0(0.00)	1.0000	0(0.00)	0(0.00)	-	0(0.00)	0(0.00)	-
Arthralgia	0(0.00)	0(0.00)	-	2(1.56)	0(0.00)	1.0000	2(3.45)	1(5.88)	0.5430	-	-	-

Irritability, sleepiness, and arthralgia were evaluated only for subjects <12 yr of age, Fatigue was evaluated only for subjects ≥5 yr of age
Difference between treatment groups († chi-square test, †† Fisher's exact test)

- Unsolicited Adverse drug Reactions(ADR)

Unsolicited (SOC/PT)	6 months ≤ Age < 3 years NBP607-QIV	Comparator	3 years ≤ Age < 9 years NBP607-QIV	Comparator	9 years ≤ Age ≤ 18 years NBP607-QIV	Comparator
N	110	25	128	31	127	32
Infections and Infestations	3(2.73)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Nasopharyngitis	3(2.73)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

- Serious Adverse Event (SAE)

- No SAEs were related to the investigational product, and all occurred SAEs were recovered

	6 months ≤ Age < 3 years		3 years ≤ Age < 9 years		9 years ≤ Age ≤ 18 years		Total	
	NBP607-QIV	Comparator	NBP607-QIV	Comparator	NBP607-QIV	Comparator	NBP607-QIV	Comparator
N	110	25	128	31	127	32	366	88
SAE incidence	4(3.64)	3(12.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	4(1.10)	3(3.41)
SAE cases	6	3	0	0	0	0	6	3

Conclusion

- The immunogenicity of NBP607-QIV for A/H1N1, A/H3N2, B/Yamagata and B/Victoria strain sufficiently satisfied the CHMP criteria, and it was also confirmed that NBP607-QIV is a quadrivalent cell culture-derived influenza vaccine with high immunogenicity and safety comparable to the egg-derived TIV

- This study studied was sponsored by SK Chemicals Life Science Biz