Safety & Immunogenicity Results Using Needle Free Injection Systems

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Summary of Safety Study & Immunogenicity Study Results from Clinical Studies and Research

Summary of Safety, Tolerability and Immunogenicity / Seroconversion results from clinical trials / literature studies conducted using Needle Free Injection System.

1. **Safety, Tolerability and Acceptability Study of Needle-Free Injection System Vs. Conventional Hypodermic Needle, India**
   - Saline was administered to approximately 60 volunteers.
   - IntegriMedical's Needle Free Injection System (NFIS) is safe, tolerable & acceptable.
   - No significant difference in terms of tenderness, redness, induration, vital & systemic examination parameters.
   - Following is the table comparing Vas Score for Needle-Free injection and Convention Hypodermic Needle Injections.

Pain Score (Vas Score)		NF Injection (N=30)	CHN Injection (N=30)
		No. (%) of Subjects	
None	(0)	77%	30.0%
Mild	(1,2, or 3)	23%	70.0%
Moderate	(4,5, or 6)	0.0%	0.0%
Severe	(7,8,9, or 10)	0.0%	0.0%

2. **Immunogenicity & Safety Study, India**
   - Covid Vaccine (Covishield)
   - Vaccine was administered in adults and children using the needle-free injection system.
   - The immunogenicity levels using the needle free injection was at par or better than the conventional hypodermic needle.
   - Safety, acceptability and tolerability were observed in children and 47% children experienced zero pain using the needle free injections.
   - Following is the table comparing the immunogenicity levels –

Table 4: Summary statistics of concentration of IgG, IgA, and IgM

Immunological Parameters		Group T1 (N=71)			Group T2 (NFIS) (N=67)		
		Pre Dose	Post Dose	P-value (paired t-test)	Pre Dose	Post Dose	P-value (paired t-test)
IgG concen.	Mean	1083.32	1296.77	0.000	1107.93	1306.75	0.000
	STDEV	174.86	198.32		211.61	197.35	
IgA concen.	Mean	193.24	304.08	0.000	188.88	282.95	0.000
	STDEV	64.32	66.74		63.11	77.02	
IgM concen.	Mean	119.80	197.01	0.000	124.24	189.37	0.000
	STDEV	50.32	55.42		57.10	49.24	

*** Group T1 - Hypodermic Needle,
Group T2 – Needle Free Injection System

3. **Immunogenicity & Safety Study, India (Bavdekar 2018) –**
   - MMR Vaccine - Randomized, parallel group, non-inferiority trial
   - Multicentric clinical study was conducted and MMR Vaccine was administered subcutaneously in the anterolateral aspect of the thigh region.
   - On evaluation of the immunogenicity results, it was observed that at baseline, seropositivity rates were similar between both the groups for all three antigens. On day 35, seropositivity rates on day 35 are as shown in table below:

Vaccine component		Day 35	
		DSJI (n = 161)	N-S (n = 157)
Measles	Seropositive subjects (%) 2-Sided 95% CI	157 (97.5) (93.8, 99.3)	155 (98.7) (95.5, 99.8)
Mumps	Seropositive subjects (%) 2-Sided 95% CI	159 (98.8) (95.6, 99.8)	155 (98.7) (95.5, 99.8)
Rubella	Seropositive subjects (%) 2-Sided 95% CI	159 (98.8) (95.6, 99.8)	157 (100.0) (97.7, 100.0)

   - Conclusion: MMR vaccination via DSJI is as immunogenic as vaccination by N-S.

4. **Immunogenicity and Tolerance Study, USA (McAllister L, 201)**
   - Influenza vaccine - Afluria
   - Vaccine was delivered by needle-free injection and compared with standard syringe injection to 1247 adults and immunogenicity results are as follows –

Immunogenicity for different type of influenza vaccine and AEs (28 days post vaccination)

Seroconversion rate, %	**NFJI**	**N-S**	**Rate difference (95%CI)**
H1N1	37.5	38.4	0.8 (-4.8, 6.5)
H3N2	43.8	45.1	1.3 (-4.5, 7.1)
B	34.9	35.2	0.3 (-5.5, 5.9)
GMT	**NFJI**	**N-S**	**Rate ratio (95%CI)**
H1N1	282.9	280.6	0·99 (0·8–1·12)
H3N2	247.3	265.9	1·08 (0·96–1·21)
B	42.5	39.7	0·94 (0·83–1·06)
AEs	**NFJI**	**N-S**	**Rate difference (95%CI)**
Local AEs on day 0, %	47.3	17.2	Not reported
Solicited AEs, day 0-6, %	95.1	85.0	Not reported
Systemic AEs	Not reported	Not reported	No significant difference

   - The immune response to influenza vaccine given with the jet injector device was non-inferior to the immune response to influenza vaccine given with needle and syringe.
   - Moreover, jet injection needle free administration addresses needle fear and the safety risks for patients and health-care providers associated with traditional administration of vaccines by needle and syringe.

5. **Immunogenicity and Tolerance Study, USA (Simon JK, 2011)**
   - Sixty healthy adults received one 0.5 mL intramuscular dose of the 2009–2010 seasonal, trivalent, inactivated influenza vaccine (TIV) in randomized, double-masked fashion by either DSJI (n = 30) or N–S (n = 30)
   - DSJI delivery of TIV is well-tolerated and immunogenic and results are as follows –

H1N1	DSJI	N-S	p^a
GMT[b] day 0 (95% CI[c])	17(11–26)	30(18–50)	0.1
GMT day 28 (95% CI)	213(127–357)	199(131–301)	0.8
Seroconversion: Percent ≥4-fold rise from day 0 to day 28 (95% CI)	80(65–95)	63(45–81)	0.3
Seroprotection: Percent HI titer ≥40 on day 28 (95% CI)	83(69–97)	90(79–100)	0.5
H3N2			
GMT[b] day 0 (95% CI[c])	31(18–52)	30(16–54)	0.9
GMT day 28 (95% CI)	426(253–717)	301(177–511)	0.3
Seroconversion: Percent ≥4-fold rise from day 0 to day 28 (95% CI)	80(65–95)	67(49–84)	0.4
Seroprotection: Percent HI titer ≥40 on day 28 (95% CI)	100(NA)	93(84–100)	0.5
B			
GMT[b] day 0 (95% CI[c])	14(9–19)	19(14–28)	0.1
GMT day 28 (95% CI)	111(71–175)	131(83–206)	0.6
Seroconversion: Percent ≥4-fold rise from day 0 to day 28 (95% CI)	73(57–90)	57(38–75)	0.3
Seroprotection: Percent HI titer ≥40 on day 28 (95% CI)	77(61–92)	87(74–99)	0.5

6. **Immunogenicity and Tolerance Study, Australia (Petrovsky N, 2013)**
   - 46 predominantly elderly subjects were randomized 1:1 to receive Fluvax 2012 trivalent inactivated influenza vaccine via prefilled N–S or DSJI
   - A high frequency of subjects in the DSJI group (77.3%) reported no anxiety or fear.
   - The device generated good vaccine immunogenicity, was easy to use with minimal training, and was well accepted by the majority of subjects.
   - Immunogenicity results are as follows:

Table 2
Vaccine efficacy.

	N–S (95% CI)	DSJI (95% CI)
A/California/7/2009 (H1N1)		
GMT (pre/post)	29.1/75.5	34.2/80.0
Seroconversion	33.3% (14.4–52.2)	31.8% (12.3–51.3)
Seroprotection	79.2% (63.0–95.4)	86.4% (72.1–100)
GMT fold increase	2.6 (1.4–3.8)	2.3 (1.3–3.4)
A/Perth/16/2009 (H3N2)		
GMT (pre/post)	23.8/42.4	23.4/49.9
Seroconversion	12.5% (0.7–25.7)	31.8% (12.3–51.3)
Seroprotection	66.7% (47.8–85.6)	72.7% (54.1–91.3)
GMT fold increase	1.8 (1.0–2.6)	2.1 (1.1–3.2)
B/Brisbane/60/2008		
GMT (pre/post)	11.2/16.8	15.5/22.0
Seroconversion	4.1% (3.8–12.0)	4.5% (4.2–13.2)
Seroprotection	16.7% (1.8–31.6)	18.2% (2.1–34.3)
GMT fold increase	1.5 (0.9–2.1)	1.4 (0.7–2.2)

7. Immunogenicity and Tolerance Study, France & Africa (Isabelle Parent du Chfitelet 1997)

- DTP Vaccine
- Vaccine was delivered by needle-free injection and compared with standard syringe injection and immunogenicity results are as follows –

Type of Antigen	Diphtheria		Tetanus		Pertussis	
	Imule (Needle Free)	Syringe	Imule (Needle Free)	Syringe	Imule (Needle Free)	Syringe
Pre-vaccinal GMT (IU ml-')	0.05 (0.04-0.68)	0.07 (0.06-0.08)	0.09 (0.07-0.12)	0.17 (0.12-0.23)	10.6 (7.6-14.5)	9.7 (7.1-13.3)
Post-vaccinal GMT (IU ml-')	0.55 (0.44-0.69)	0.34 (0.27-0.41)	2.27 (2.12-2.43)	1.46 (1.29-l .65)	1434 (1188-l 732)	1188 (965-l 465)
Seroconversion %	79.2%	56.7%	88.7%	70.3%	94.4%	94.6%

*GMT = Geometric Mean Titter

- Similar study was conducted on Pentavalent diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA), and Haemophilus influenzae type b conjugate vaccine administered with needle-free injections. Seropositivity rates for the DSJI and N-S groups in the per-protocol population at baseline and at day 84 post vaccination appeared comparable, by descriptive statistics, for all vaccine components.
- Table below provides Seroprotection/Seropositivity at days 0 and 84 after vaccination:

Vaccine component	Day 0		Day 84	
	DSJI (n = 61)	N-S (n = 67)	DSJI (n = 61)	N-S (n =67)
Diphtheria	4 (6.6%)	7 (10.4%)	61 (100.0%)	64 (95.5%)
Tetanus	61 (100.0%)	66 (98.5%)	61 (100.0%)	66 (98.5%)
Pertussis	3 (4.9%)	1 (1.5%)	36 (59.0%)	41 (61.2%)
Hepatitis B	9 (14.8%)	9 (13.4%)	60 (98.4%)	66 (98.5%)
Haemophilus influenzae type B (long- term protection)	21 (34.4%)	24 (35.8%)	56 (91.8%)	62 (92.5%)
Haemophilus influenzae type B ≥0.15 µg/mL (short-term protection)	48 (78.7%)	55 (82.1%)	61 (100.0%)	65 (97.0%)