ANALYSIS OF SPECIFIC ANTIBODY LEVELS IN PIDD PATIENTS ENROLLED IN A PIVOTAL TRIAL WITH AN IVIG CONTAINING HIGH TITER NEUTRALIZING ANTIBODY TO RSV

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Introduction

Immunoglobulin G (IG) purified from normal donor plasma pools effectively replaces the absent humoral antibody compartment in PIDD patients. The concentration of specific anti-pathogen antibodies in the IG may be limiting particularly when there are high loads of the offending organism. We have recently completed a phase III trial of the investigational product RI-002 in 59 subjects with PIDD. The primary outcome was the prevention of serious bacterial infections. This is an IVIG derived from plasma donors selected for their high titers of neutralizing antibodies to RSV. RI-002 also contains high titers of antibodies to other respiratory viruses. The data presented evaluates the increases in specific anti-pathogen antibody titers observed in the patients after receiving RI-002, the dose relationship of these increases and whether there is a correlation between the levels of antibodies and the incidence of non-serious bacterial infections in these patients.

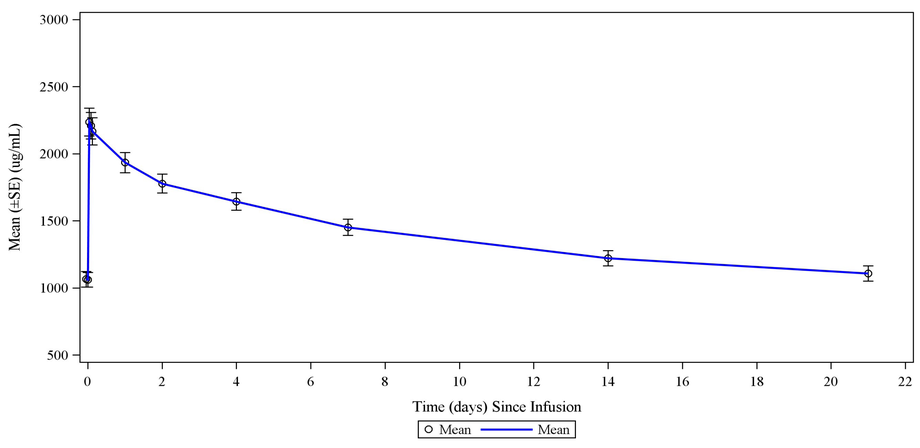
Patient Demographics in the Phase III Trial with RI-002

Characteristic/ Statistics	Total (Subjects=59)	3-Week Cycle (Subjects=19)	4-Week Cycle (Subjects=40)
Age (years)			
N	59	19	40
Mean (SE)	41.8 (2.84)	38.6 (4.94)	43.3 (3.48)
SD	21.78	21.53	22.01
Min, Max	3, 74	5, 70	3, 74
Age Group			
2-6 years	2 (3.4%)	1 (5.3%)	1 (2.5%)
7-11 years	4 (6.8%)	1 (5.3%)	3 (7.5%)
12-16 years	5 (8.5%)	1 (5.3%)	4 (10.0%)
>16 years	48 (81.4%)	16 (84.2%)	32 (80.0%)
Sex			
Male	28 (47.5%)	7 (36.8%)	21 (52.5%)
Female	31 (52.5%)	12 (63.2%)	19 (47.5%)

Summary of Unscheduled Medical Visits and Days Missed from Work/School/ Daycare Due to Infection

Summary Category	Total (Subjects=59)	3-Week Cycle (Subjects=19)	4-Week Cycle (Subjects=40)
Unscheduled Medical Visits Due to Infection			
Total Visits in the study	54	18	36
Visits per person per year	**0.966**	1.041	0.933
1-Sided 95% Upper Bound	1.209	1.533	1.227
Number of Days Lost from Work/School/Day Care Due to Infections			
Total days missed in the study	93	27	66
No. of days missed per person per year	**1.66**	1.56	1.71
1-Sided 95% Upper Bound	0.197	2.14	2.0

Pharmacokinetics of Immunoglobulin: Concentration Over Time

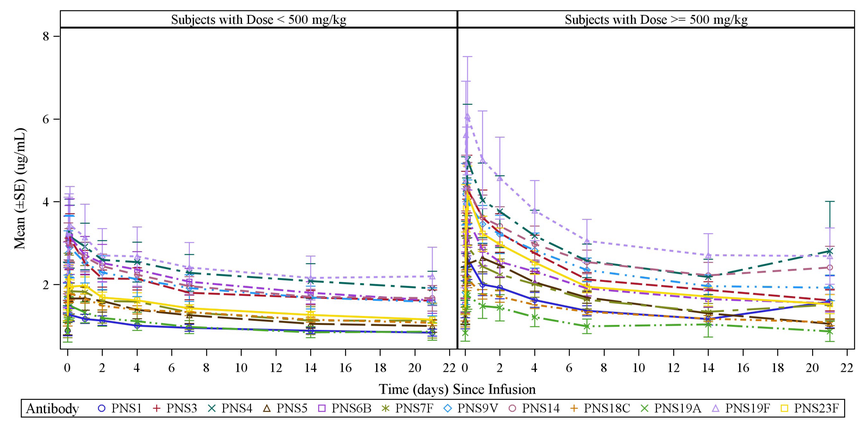


Antibody Titer Cmax and Cmax Fold Change from Baseline Post Infusion

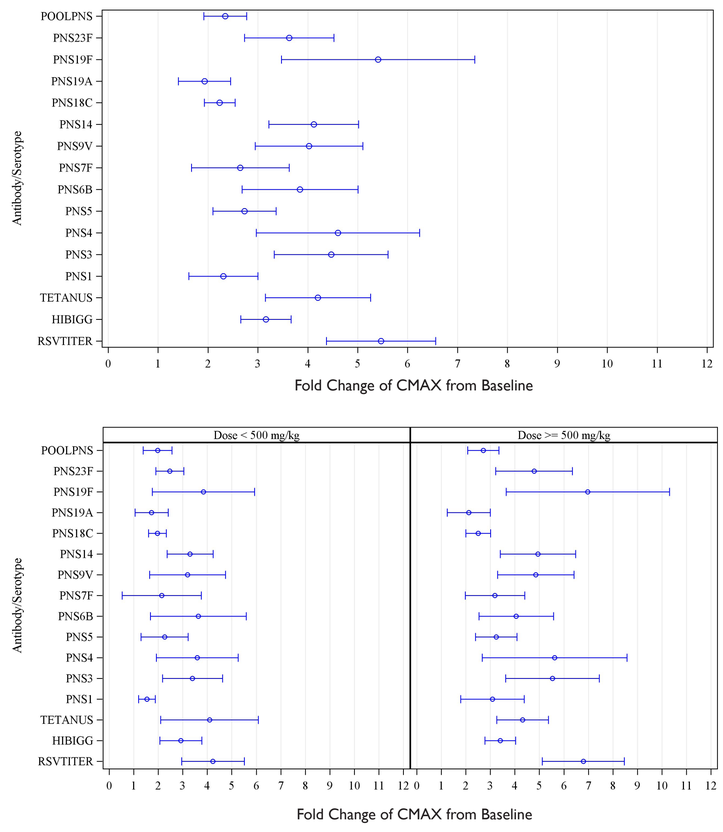
	All Subjects [1]		All Subjects [1]		All Subjects [1]			Doses < 500 mg/kg [2]			Doses ≥ 500 mg/kg [2]		
	Baseline		Cmax		Cmax/Baseline			Cmax/Baseline			Cmax/Baseline		
Antibody	Mean	SE	Mean	SE	Mean	SE	P-value[3]	Mean	SE	P-value[3]	Mean	SE	P-value[3]
RSV	1260.00^	272.89	4770.2	392.03	5.47^	0.53	<.0001	4.23	0.60	<.0001	6.79§	0.78	<.0001
HIBIGG	2.58	0.23	6.96	0.32	3.16	0.25	<.0001	2.92	0.40	0.0003	3.4	0.29	<.0001
TETANUS	6.81	1.04	21.23	1.28	4.2	0.52	<.0001	4.09	0.93	0.0050	4.32	0.49	<.0001
MEASLES [4]	2976.7	660.14	5703.13	771.94	2.93	0.27	<.0001	2.68	0.41	0.0012	3.18	0.35	<.0001
CMV[4]	773.43	164.74	1881.57	257.04	3.17	0.29	<.0001	2.88	0.32	<.0001	3.46	0.48	0.0001
PNS4	0.53	0.11	1.49	0.15	4.61	0.80	<.0001	3.59	0.78	0.0049	5.62	1.38	0.0047
PNS5	12.13^	1.08	27.69	1.87	2.73^	0.31	<.0001	2.26	0.45	0.0138	3.24§	0.39	<.0001
PNS6B	1.82	0.28	5.22	0.50	3.84	0.57	<.0001	3.63	0.91	0.0119	4.05	0.71	0.0007
PNS7F	3.42^	0.58	5.36	0.43	2.65^	0.48	0.0018	2.14	0.75	0.1528	3.19§	0.56	0.0018
PNS9V	1.37	0.13	4.25	0.32	4.02	0.53	<.0001	3.2	0.72	0.0088	4.85	0.73	0.0001
PNS14	4.04	0.34	13.34	0.63	4.12	0.44	<.0001	3.3	0.44	0.0001	4.94	0.72	<.0001
PNS18C	6.05	0.52	12.29	0.85	2.23	0.15	<.0001	1.97	0.17	<.0001	2.5	0.24	<.0001
PNS19A	20.14$	2.65	29.21	2.13	1.93$	0.25	0.0012	1.73%	0.31	0.0367	2.12&	0.40	0.0171
PNS19F	7.02	1.58	17.67	1.26	5.41	0.95	<.0001	3.84	0.97	0.0113	6.97	1.55	0.0018
PNS23F	1.5	0.2	4.28	0.33	3.62	0.44	<.0001	2.47	0.27	<.0001	4.78	0.73	0.0001
Pooled PNS	5.05	0.41	10.01	0.42	2.35	0.21	<.0001	1.98	0.27	0.0031	2.72	0.30	<.0001

[1] n=30 for all analyses except ^n=29, $n=25; [2] n=15 for all analyses except §n=14, &n=13, %n=12; [3] P-value from Student's t-test for null hypothesis of no change. [4] Cmax for Measles and CMV were compared to pre-infusion titer;

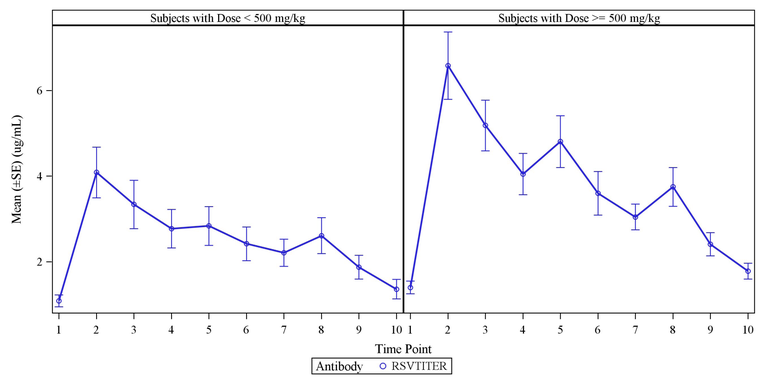
S. Pneumococcal Titer Over Time - by Serotype and Dose



Fold Increase in Specific Antibody Levels After Infusion of RI-002



RSV Titer Fold Change from Baseline Over Time by Dose



Time Point: 0=Baseline; 1=Pre-Infusion; 2=End of Infusion; 3=60 Min. Post; 4=2 Hrs Post; 5=24 Hrs Post 6=48 Hrs Post; 7=4 Days Post; 8=7 Days Post; 9=14 Days Post; 10=21Days Post

Distribution of All Infections and Infection Events of Interest By Actual Weight Adjusted Infusion Dose mg/kg

Infection Events [1]	Weight Adjusted Actual Dose	No. of AEs [A]	No. of Infusions [B]	No. of AEs per Infusion [A/B]
All Infections	All Doses	192	793	0.2421
	Dose < 500 mg/kg	122	436	0.2798
	Dose >=500 mg/kg	70	357	0.1961
Bronchitis	All Doses	14	793	0.0177
	Dose < 500 mg/kg	10	436	0.0229
	Dose >=500 mg/kg	4	357	0.0112
Chronic + Acute Sinusitis	All Doses	46	793	0.0580
	Dose < 500 mg/kg	27	436	0.0619
	Dose >=500 mg/kg	19	357	0.0532
Otitis media	All Doses	1	793	0.0013
	Dose < 500 mg/kg	1	436	0.0023
	Dose >=500 mg/kg	0	357	0.0000
Influenza	All Doses	5	793	0.0063
	Dose < 500 mg/kg	3	436	0.0069
	Dose >=500 mg/kg	2	357	0.0056
Nasopharyngitis	All Doses	26	793	0.0328
	Dose < 500 mg/kg	17	436	0.0390
	Dose >=500 mg/kg	9	357	0.0252
URI	All Doses	29	793	0.0366
	Dose < 500 mg/kg	13	436	0.0298
	Dose >=500 mg/kg	16	357	0.0448

[1] Infection events used the following definitions:
1) Bronchitis included AE referred term of Bronchitis.
2) Chronic + acute sinusitis included AE referred terms of Acute sinusitis and Sinusitis.
3) Nasopharyngitis included AE referred terms of Nasopharyngitis, Pharyngitis streptococcal, and Viral pharyngitis.
4) Otitis media included AE referred terms of Otitis media.
5) URI included AE referred terms of Croup infectious, Upper respiratory tract infection, and Viral upper respiratory tract infection.

Summary

RI-002 a 10% Human immunoglobulin (IVIG) prepared with standardized elevated levels of naturally occurring anti-RSV neutralizing antibodies successfully met its primary and secondary efficacy and safety objectives in a phase III trial in 59 patients with PIDD. There were zero serious bacterial infections, a total of only one SAE due to infection, only 1.66 days per subject per year were lost from work, school or day care due to infection and only 0.097 days per subject per year of unscheduled visits to the physician or ER. Patients receiving doses greater than 500mg/kg of RI-002 had higher levels of anti S. pneumococcal antibody of all the serotypes measured as compared to those receiving less than 500mg/kg. There was an average of a 5 fold increase in levels of anti RSV neutralizing antibody and a 2-4 fold rise in concentrations of all specific antibodies measured after infusion of the IG, with a trend of greater increases in those who were on the 4 weeks cycle of infusions as compared to the three week infusions. There was a trend of fewer infections of interest seen in the group receiving the higher doses of IG.

Conclusion

RI-002 is an IVIG prepared to meet the FDA standards for immunoglobulins and contains standardized, elevated levels of RSV neutralizing antibodies. Patients receiving doses of RI-002 greater than 500mg/kg have higher concentrations of specific anti pathogen antibodies than those receiving lower doses and this may be associated with lower incidence of infections. RI-002 may provide a promising alternative to currently marketed immunoglobulins for certain patients with PIDD.