FIGURE LEGENDS

Figure 1: Consort Diagram

On the first day, dosing was initiated with 0.07mg of milk protein. Subjects were required to tolerate dose #6 (2.1mg) at dosing visit 1 and dose #8 (9mg) by visit 2. Daily home dosing was continued and subjects returned every 2 weeks for dose escalation for a minimum of 22 and a maximum of 40 weeks. Subjects were required to reach a minimum maintenance dose of 520mg milk protein (equivalent to 15mL of liquid milk).

Figures 2a – 2d: Figures 2a&b: Casein and Beta-lactoglobulin IgG4 Levels: Casein and beta-lactoglobulin specific IgG4 levels were measured at baseline and months 4, 16, 22, 28, 30, and 32. Median values are represented by the blue stars. Significant increases from baseline were detected within both treatment groups from month 16 onward (all $P<0.0001$), with no differences seen between the two groups. **Figures 2c&d: Casein and Beta-lactoglobulin IgG4/IgE Ratio:** The ratio of casein- and β-lactoglobulin IgG4/IgE was calculated after IgG4 levels were converted from mg_A/L to ng/mL and IgE level was converted from kU_A/L to ng/mL with the formula (IgG4 × 1000) ÷ (IgE × 2.4). Significant increases from baseline were detected within both treatment groups from month 16 onward (all $P<0.0001$). The only significant difference between treatment groups was observed at month 4 with omalizumab subjects exhibiting decreased casein and beta-lactoglobulin IgG4/IgE ratio compared to placebo subjects.

Supplemental Figures 1a, 1b & 1c: Milk, Casein, and Beta-lactoglobulin IgE Levels: Milk, casein, and beta-lactoglobulin specific IgE levels were measured at baseline and months 4, 16, 22, 28, 30, and 32. Median values are represented by the blue stars. In the placebo group, after a non-significant increase

in milk IgE at month 4, milk and casein IgE levels were significantly reduced at all subsequent time points and beta-lactoglobulin IgE did not significantly change. In the omalizumab group, milk and casein IgE were significantly increased at month 4 and reduced at month 32 and beta-lactoglobulin IgE was significantly increased at month 4 and month 16 compared to baseline. Comparing the treatment groups, there were significant differences in the change from baseline for milk IgE through month 30, for casein IgE through month 28 and for beta-lactoglobulin IgE through month 22.

Supplemental Figures 1d & 1e: Casein and β-lactoglobulin IgG Levels: Casein and β-lactoglobulin specific IgG levels were measured at baseline and months 4, 16, 22, 28, 30, and 32. Median values are represented by the blue stars. Significant increases from baseline were detected within both treatment groups from month 16 onward (all $P<0.0001$), with no differences seen between the two groups.

Supplemental Figure 2: Milk Endpoint Skin Prick Test Titration: Skin prick test endpoint titrations were conducted at baseline and months 28 and 32. Both groups exhibited a significant change from baseline ($P<0.0001$ at months 28 and 32) but there was no difference between the groups in change from baseline at any of the three time points.

Supplemental Figure 3: Basophil Activation by Treatment Group: Basophil activation was assessed at baseline and months 4, 16, 22, 28, 30, and 32. A repeated measures analysis of percent CD63+ cells over time through month 32 found a decrease in the omalizumab group compared to the placebo through month 28, after which values for omalizumab increased until they were similar to placebo at month 32 such that the interaction between treatment and visit was statistically significant (interaction term for 10 μg/mL milk: $p<0.0001$, interaction term for 1 μg/mL milk: $p=0.009$). At the 0.1 μg/mL milk stimulant level, similar trends were seen, but the interaction term was not significant; the p-value for the

405 treatment effect was significant (p=0.003). At the 0.01 μg/mL and 0.001 μg/mL milk stimulant levels, no

406 statistically significant differences were seen.

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Supplemental Table 1: Milk OIT Dosing Scheme

Dose #	Dose milk protein (mg)	Dose milk powder (mg)	% Increase per dose	% Increase per day	Cumulative dose milk powder (mg)
Dose Visit 1					
1	0.07	0.2			0.2
2	0.15	0.4	100%		0.6
3	0.28	0.8	100%		1.4
4	0.53	1.5	100%		2.9
5	1.1	3.0	100%		5.9
6	2.1	6.0	100%	N/A	11.9
Dose Visit 2					
7	4	12	100%		12
8	9	25	100%		37
9	18	50	100%		87
10	27	75	50%	2566%	162
Dose Visit 3					
11	36	100	25%		100
12	44	125	25%		225
13	56	156	25%		381
14	69	195	25%	668%	576
Dose Visit 4					
15	87	245	25%		245
16	109	306	25%		551
17	136	383	25%		934
18	170	479	25%	625%	1413
Dose Visit 5					

19	213	599	25%		599
20	267	749	25%		1348
21	333	936	25%		2284
22	416	1170	25%	621%	3454
Dose Visit 6					
23	520	1463	25%		1463
24	650	1829	25%	181%	3292
Dose Visit 7					
25	814	2286	25%		2286
26	1017	2858	25%	181%	5144
Dose Visit 8					
27	1352	3801	33%	33%	3801
Dose Visit 9					
28	1799	5055	33%	33%	5055
Dose Visit 10					
29	2392	6723	33%	33%	6723
Dose Visit 11					
30	2990	8404	25%	25%	8404
Dose Visit 12					
31	3300	9281	10%	10%	9281
by Scoop	3840	10800	16%	16%	10800

Supplemental Table 2: Specific Challenge Outcomes at Baseline, Month 28 and Month 32

			Omalizumab	Placebo	Total
Successfully Consumed Dose (mg milk protein)	**Baseline (2 g OFC)**	**N**	28	29	57
		Mean	75.0	118.3	97.0
		Median	20.0	10.0	20.0
		Lower Quartile	0.0	0.0	0.0
		Upper Quartile	100.0	100.0	100.0
		StdErr	27.2	55.5	31.1
		Min	0.0	0.0	0.0
		Max	720.0	1500.0	1500.0
	Month 28 (10g Desensitization OFC)	**N**	26	24	50
		Mean	9653.8	9337.5	9502.0
		Median	10000.0	10000.0	10000.0
		Lower Quartile	10000.0	10000.0	10000.0
		Upper Quartile	10000.0	10000.0	10000.0
		StdErr	239.8	338.3	203.9
		Min	5500.0	3600.0	3600.0
		Max	10000.0	10000.0	10000.0
	Month 32 (10g Tolerance OFC)	**N**	24	20	44
		Mean	7541.7	7350.0	7454.5
		Median	10000.0	8750.0	10000.0
		Lower Quartile	6500.0	5500.0	5500.0

			Omalizumab	Placebo	Total
		Upper Quartile	10000.0	10000.0	10000.0
		StdErr	711.5	721.9	502.6
		Min	0.0	1500.0	0.0
		Max	10000.0	10000.0	10000.0

Supplemental Table 3. Number of Doses with Dosing Symptoms During Escalation Period

	Omalizumab		Placebo	
	N	**%**	**N**	**%**
Total # Doses	5226	100.0	6252	100.0
Any Symptoms	442	8.5	1634	26.1
Any Symptoms Excluding Oral/Pharyngeal	232	4.4	862	13.8
Duration >30 min.	60	1.1	228	3.6
Treatment Used	105	2.0	293	4.7
Oral/Pharyngeal Symptoms	320	6.1	1163	18.6
Skin Symptoms	44	0.8	165	2.6
Respiratory Symptoms	92	1.8	264	4.2
GI Symptoms	111	2.1	386	6.2
Other Symptoms	49	0.9	282	4.5
Mild Symptoms	215	4.1	806	12.9
Moderate Symptoms	17	0.3	55	0.9
Severe Symptoms	0	0.0	1	0.02
Treated with Epinephrine	1	0.0	8	0.1

Supplemental Table 4. Number of Doses with Dosing Symptoms During Maintenance Period

	Omalizumab		**Placebo**	
	N	**%**	**N**	**%**
Total # Doses	15418	100.0	13745	100.0
Any Symptoms	110	0.7	1983	14.4
Any Symptoms Excluding Oral/Pharyngeal	69	0.4	926	6.7
Duration >30 min.	26	0.2	234	1.7
Treatment Used	26	0.2	538	3.9
Oral/Pharyngeal Symptoms	53	0.3	1278	9.3
Skin Symptoms	23	0.1	265	1.9
Respiratory Symptoms	18	0.1	298	2.2
GI Symptoms	26	0.2	166	1.2
Other Symptoms	20	0.1	432	3.1
Mild Symptoms	67	0.4	902	6.6
Moderate Symptoms	2	0.0	23	0.2
Severe Symptoms	0	0.0	1	0.01
Treated with Epinephrine	1	0.0	10	0.1

Supplemental Table 5. Percent Doses Per Subject with Dosing Symptoms During Blinded Maintenance Period

	Treatment Group						
	Omalizumab			Placebo			
	Median	Lower Quartile	Upper Quartile	Median	Lower Quartile	Upper Quartile	P-value
Total # Doses	169.5	154.0	184.0	157.5	117.0	175.0	0.07
Any Symptoms	0.0	0.0	0.7	6.7	2.5	20.3	<.0001
Any Symptoms Excluding Oral/Pharyngeal	0.0	0.0	0.5	5.2	0.8	15.1	<.0001
Duration >30 min.	0.0	0.0	0.0	1.1	0.0	4.3	0.0003
Treatment Used	0.0	0.0	0.0	1.8	0.0	6.7	0.0004
Oral/Pharyngeal Symptoms	0.0	0.0	0.5	1.7	0.5	6.8	0.002
Skin Symptoms	0.0	0.0	0.0	0.9	0.0	2.5	0.0001
Respiratory Symptoms	0.0	0.0	0.0	1.8	0.0	4.5	0.0004
GI Symptoms	0.0	0.0	0.0	0.7	0.0	2.2	0.009
Other Symptoms	0.0	0.0	0.0	0.8	0.0	2.9	0.002
Mild Symptoms	0.0	0.0	0.5	4.7	0.6	15.1	0.0001
Moderate Symptoms	0.0	0.0	0.0	0.0	0.0	0.8	0.006
Severe Symptoms	0.0	0.0	0.0	0.0	0.0	0.0	1.0
Treated with Epinephrine	0.0	0.0	0.0	0.0	0.0	0.0	0.047

Supplemental Table 6. Percent Doses Per Subject with Dosing Symptoms During Unblinded Maintenance Period

	Treatment Group						
	Omalizumab (n=26)			Placebo (n=26)			
	Median	Lower Quartile	Upper Quartile	Median	Lower Quartile	Upper Quartile	P-value
Total # Doses	430.0	418.0	447.0	407.5	383.0	431.0	0.01
Any Symptoms	0.0	0.0	0.5	1.8	0.4	18.5	0.0002
Any Symptoms Excluding Oral/Pharyngeal	0.0	0.0	0.5	1.4	0.3	7.7	0.0003
Duration >30 min.	0.0	0.0	0.0	0.3	0.0	1.0	0.0005
Treatment Used	0.0	0.0	0.0	0.5	0.0	3.2	0.0004
Oral/Pharyngeal Symptoms	0.0	0.0	0.0	0.1	0.0	1.4	0.01
Skin Symptoms	0.0	0.0	0.0	0.2	0.0	1.2	0.01
Respiratory Symptoms	0.0	0.0	0.0	0.4	0.0	1.1	0.0007
GI Symptoms	0.0	0.0	0.0	0.1	0.0	0.5	0.02
Other Symptoms	0.0	0.0	0.0	0.3	0.0	2.6	0.001
Mild Symptoms	0.0	0.0	0.2	1.4	0.3	7.5	0.0003
Moderate Symptoms	0.0	0.0	0.0	0.0	0.0	0.0	0.09
Severe Symptoms	0.0	0.0	0.0	0.0	0.0	0.0	0.34
Treated with Epinephrine	0.0	0.0	0.0	0.0	0.0	0.0	0.29

Supplemental Table 7. Logistic Regression of Baseline Factors Predicting Month 32 Tolerance Success After Adjusting for Treatment

Variable	Wald Chi-square P-value	Odds Ratio	OR Lower CI	OR Upper CI
Gender	0.722	0.80	0.24	2.68
Physician Diagnosis Asthma	0.311	0.54	0.16	1.79
Allergic Rhinitis	0.338	0.54	0.15	1.91
Atopic Dermatitis	0.292	0.54	0.17	1.70
Age	0.987	1.00	0.89	1.12
Atopic Dermatitis Total Score	0.319	1.25	0.81	1.93
Milk Endpoint Titration SPT	0.011	0.90	0.83	0.98
Milk Skin Prick Test Score	0.012	0.76	0.62	0.94
OFC Successfully Consumed Dose	0.888	1.18	0.12	11.72
Log_{10} Total IgE	0.215	2.46	0.59	10.27
Log_{10} Milk IgE	0.007	0.20	0.06	0.63
Log_{10} Casein IgE	0.012	0.37	0.17	0.80
Log_{10} □-lactoglobulin IgE	0.051	0.46	0.21	1.00
% Milk IgE	0.003	0.90	0.84	0.97
% Casein IgE*	0.005	0.91	0.86	0.97
% □-lactoglobulin IgE	0.027	0.80	0.66	0.98
Log_{10} Casein IgG	0.037	0.16	0.03	0.89
Log_{10} □-lactoglobulin IgG	0.114	0.23	0.04	1.43
Log_{10} Casein IgG4	0.633	0.77	0.27	2.22
Log_{10} □-lactoglobulin IgG4	0.512	0.71	0.25	1.99
Log_{10} Casein IgG4/IgE	0.007	3.80	1.45	9.96
Log_{10} □-lactoglobulin IgG4/IgE	0.058	2.05	0.98	4.30
%CD63+ Cells: 10 µg/mL Milk	0.958	1.00	0.98	1.02

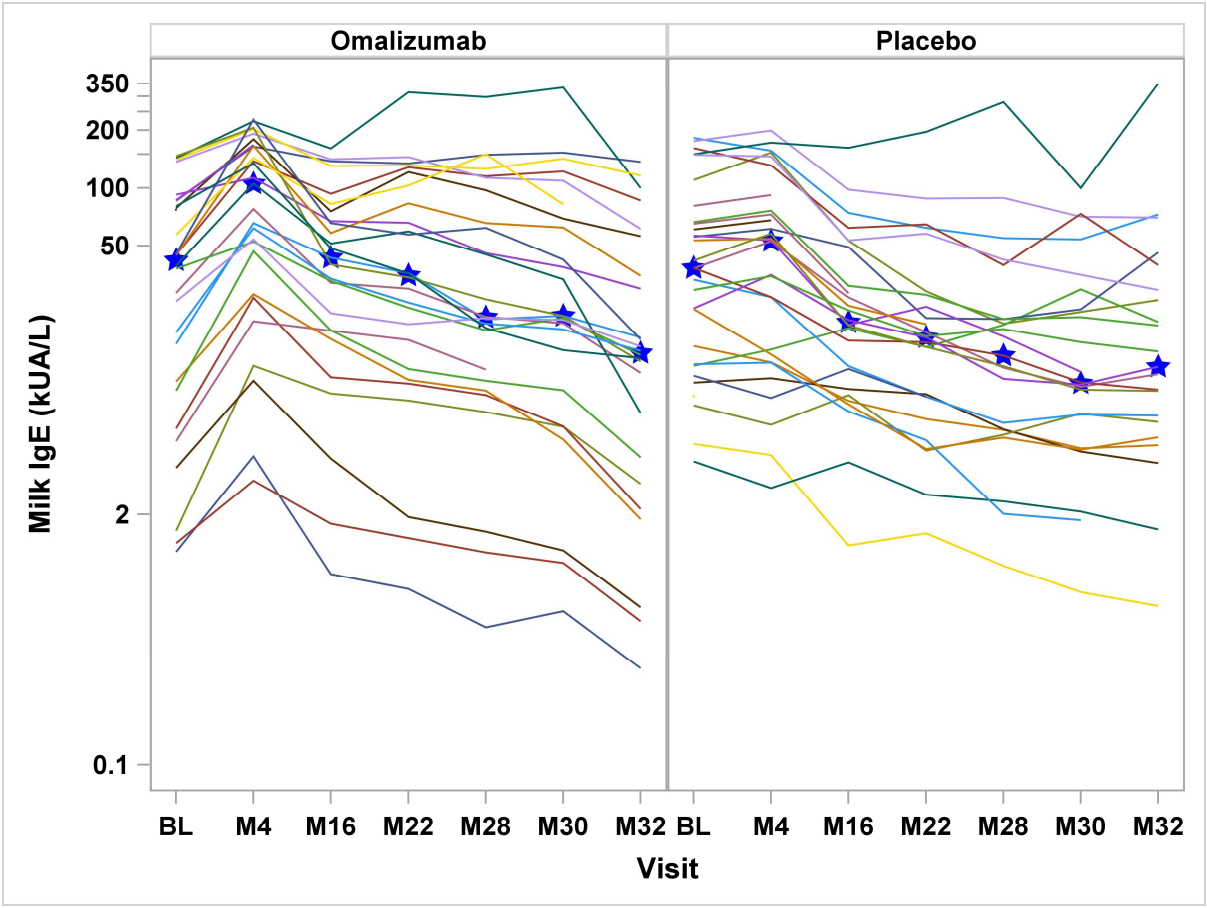
Variable	Wald Chi-square P-value	Odds Ratio	OR Lower CI	OR Upper CI
%CD63+ Cells: 1 µg/mL Milk	0.674	0.99	0.97	1.02
%CD63+ Cells: 0.1 µg/mL Milk	0.548	0.99	0.96	1.02
%CD63+ Cells: 0.01 µg/mL Milk	0.296	0.98	0.95	1.01
%CD63+ Cells: 0.001 µg/mL Milk	0.416	0.98	0.95	1.02

* Model has a statistically significant lack of fit at the 0.05 significance level.

Supplemental Table 8. Logistic Regression of Month 16 Factors Predicting Month 32 Tolerance Success After Adjusting for Treatment

Variable	Wald Chi-square P-value	Odds Ratio	OR Lower CI	OR Upper CI
Log_{10} Milk IgE	0.005	0.09	0.02	0.48
Log_{10} Casein IgE	0.012	0.28	0.11	0.75
Log_{10} β-lactoglobulin IgE	0.010	0.31	0.12	0.75
Log_{10} Casein IgG	0.026	0.31	0.11	0.87
Log_{10} β-lactoglobulin IgG	0.038	0.36	0.14	0.94
Log_{10} Casein IgG4	0.134	0.60	0.30	1.17
Log_{10} β-lactoglobulin IgG4*	0.130	0.59	0.30	1.17
Log_{10} Casein IgG4/IgE	0.061	1.72	0.98	3.03
Log_{10} β-lactoglobulin IgG4/IgE	0.066	1.74	0.96	3.16
%CD63+ Cells: 10 μg/mL Milk	0.542	1.01	0.99	1.03
%CD63+ Cells: 1 μg/mL Milk	0.472	1.01	0.98	1.04
%CD63+ Cells: 0.1 μg/mL Milk	0.577	1.01	0.97	1.05
%CD63+ Cells: 0.01 μg/mL Milk	0.445	1.02	0.97	1.06
%CD63+ Cells: 0.001 μg/mL Milk	0.120	1.15	0.96	1.36

* Model has a statistically significant lack of fit at the 0.05 significance level.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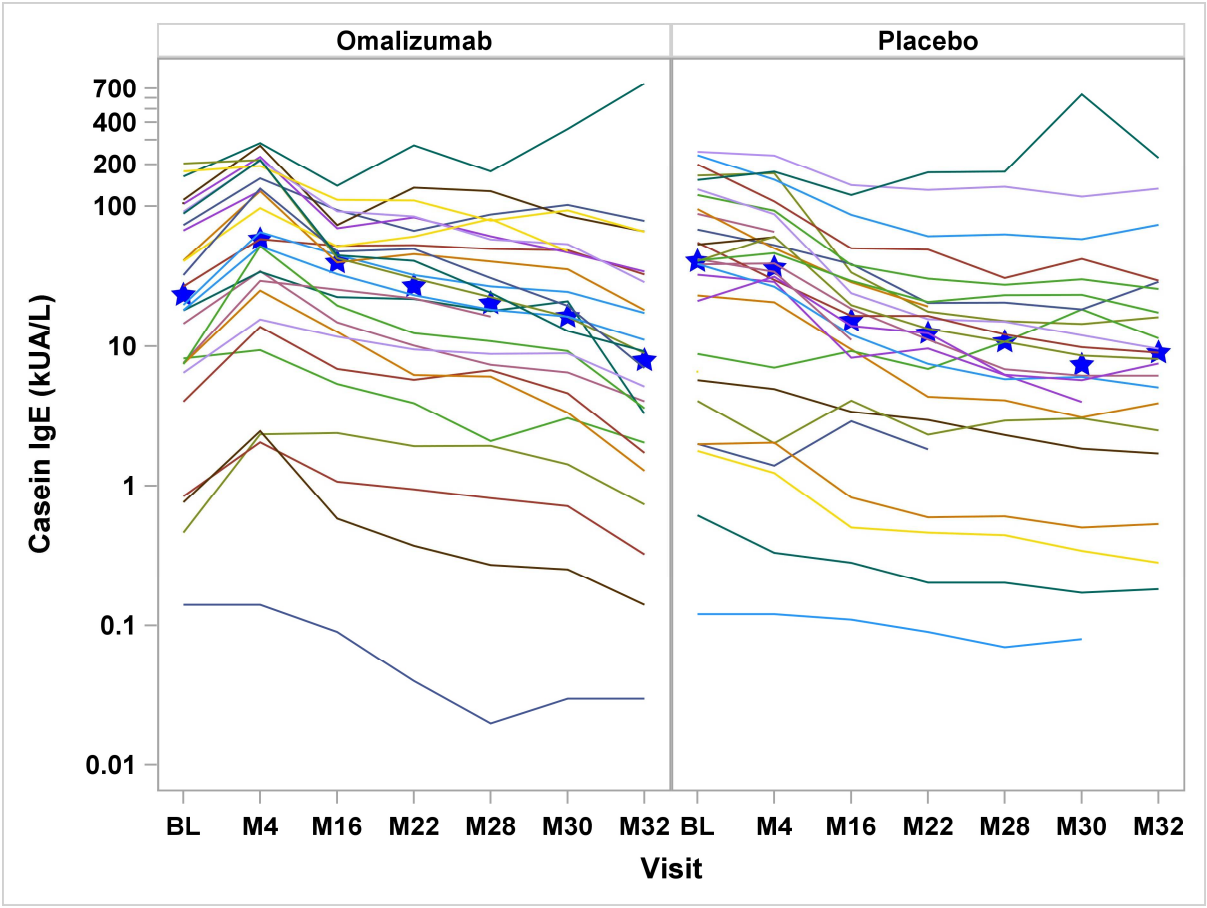
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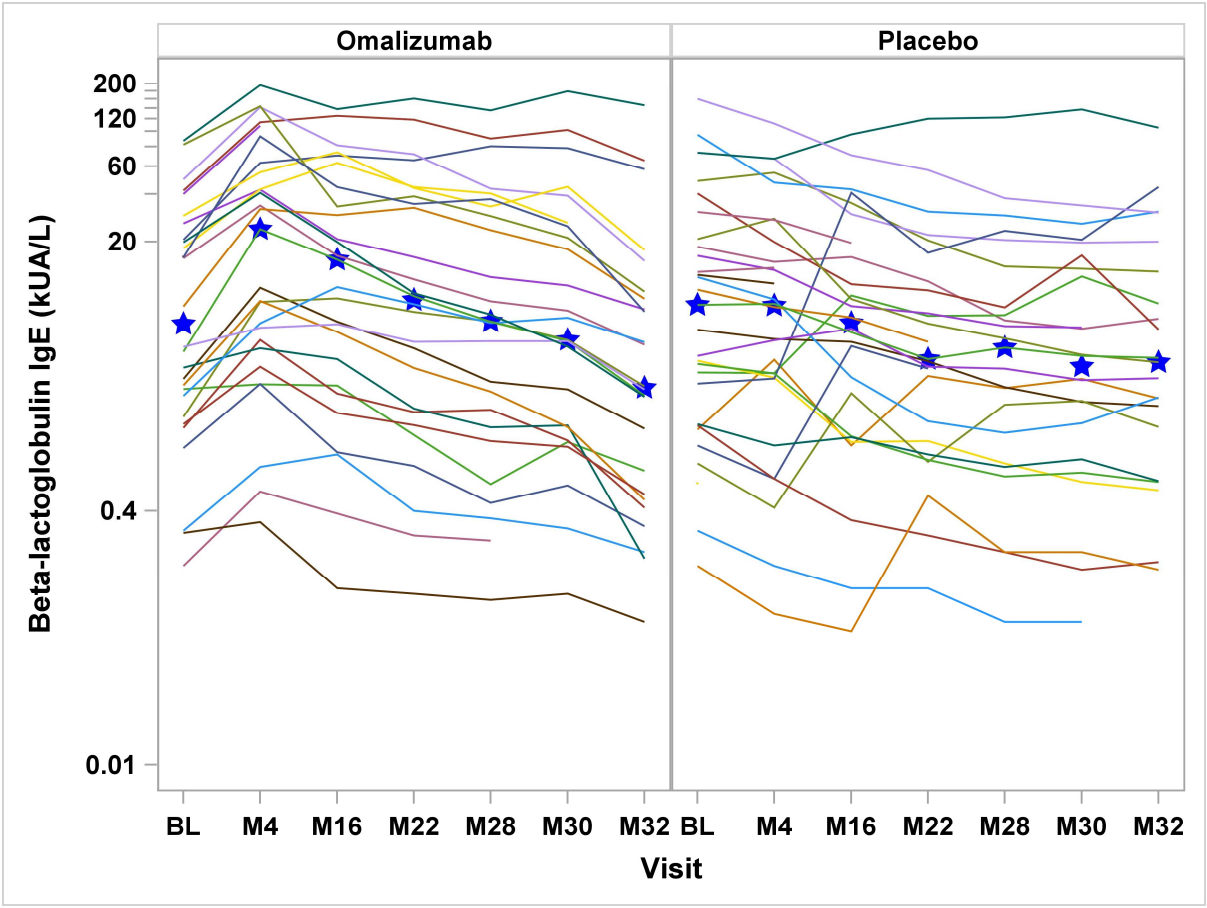
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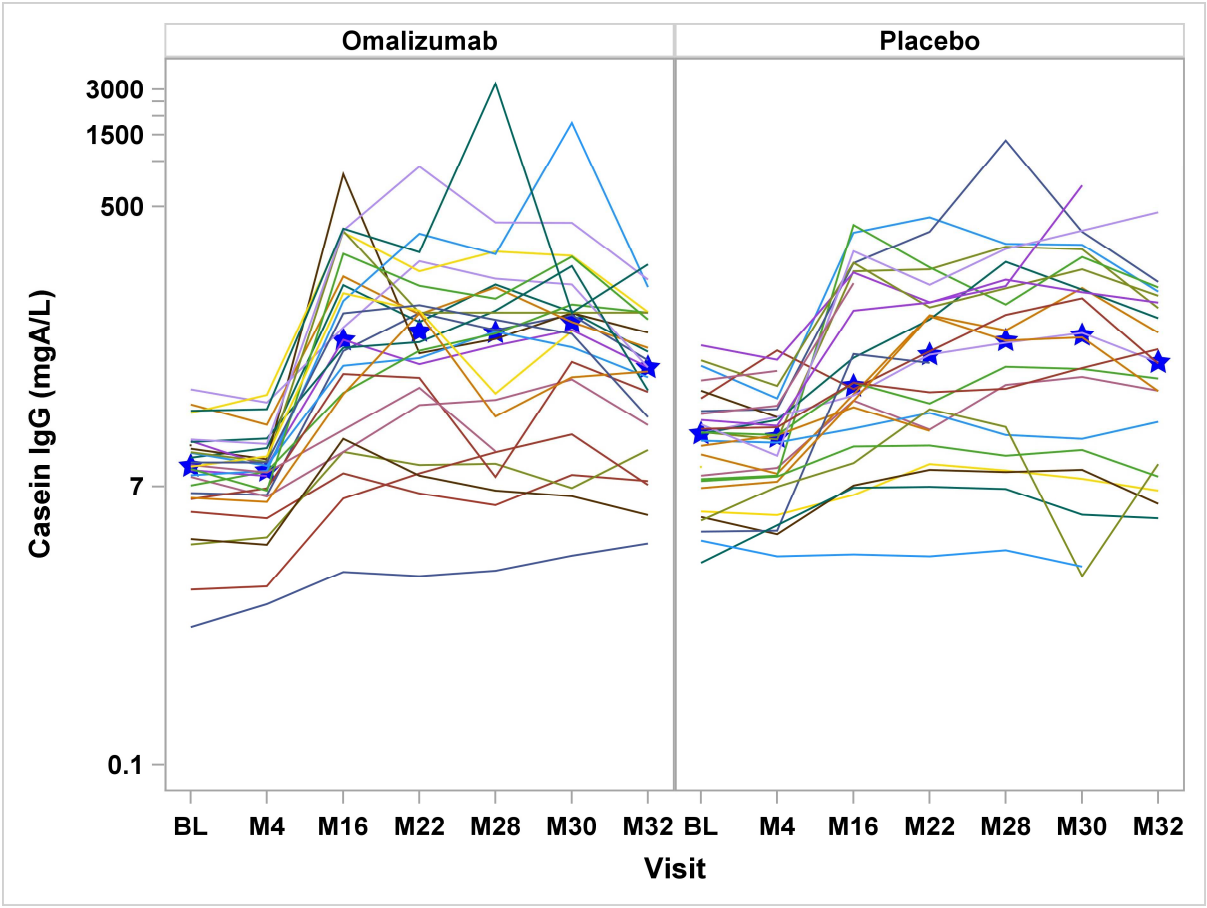
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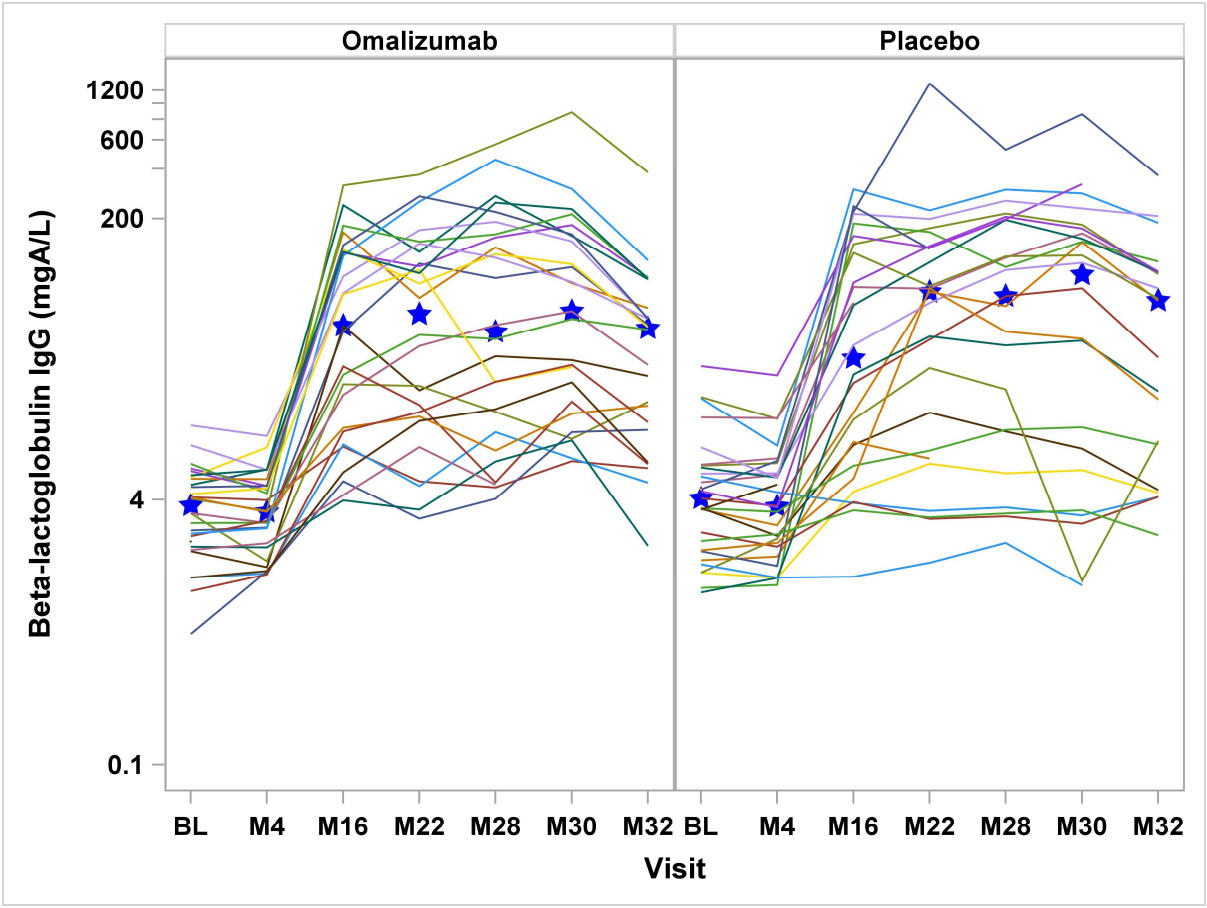
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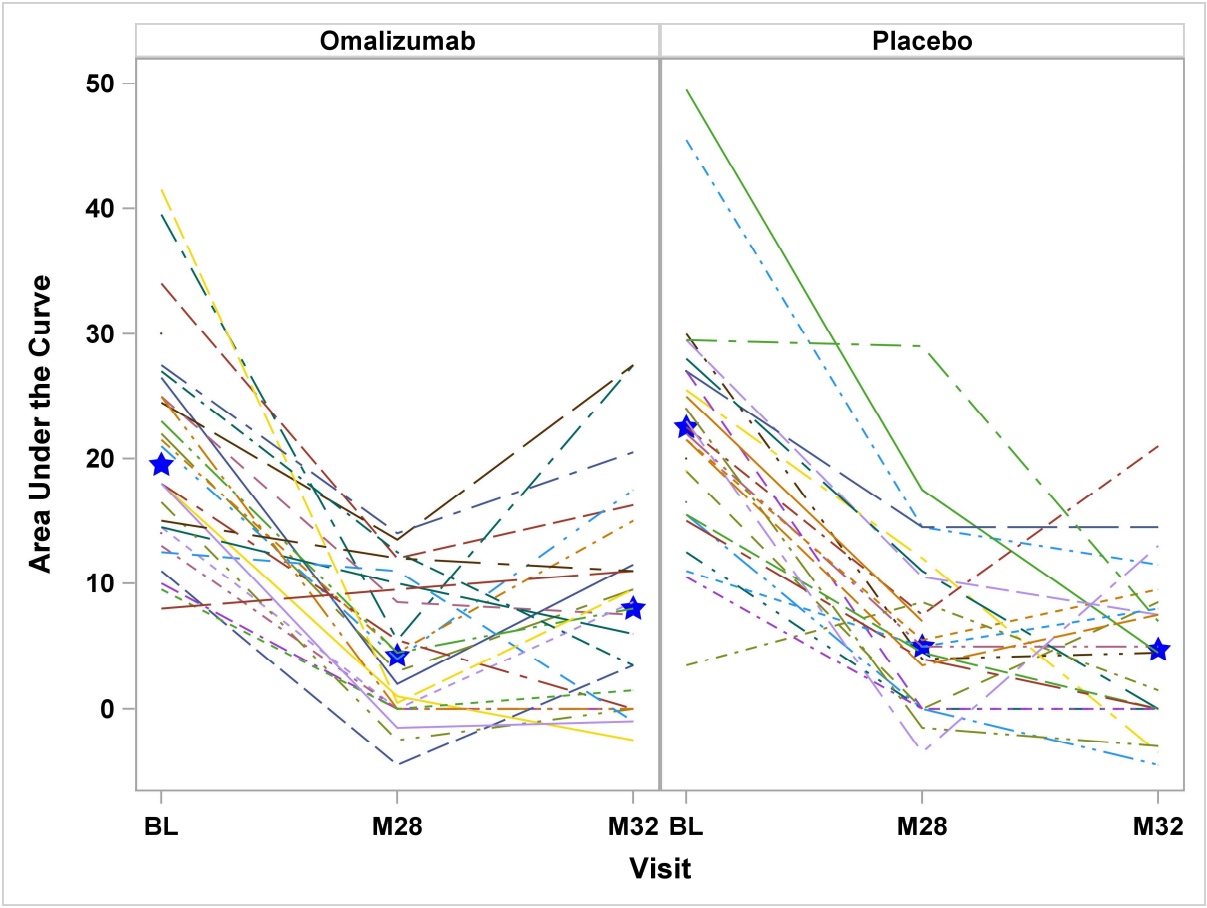
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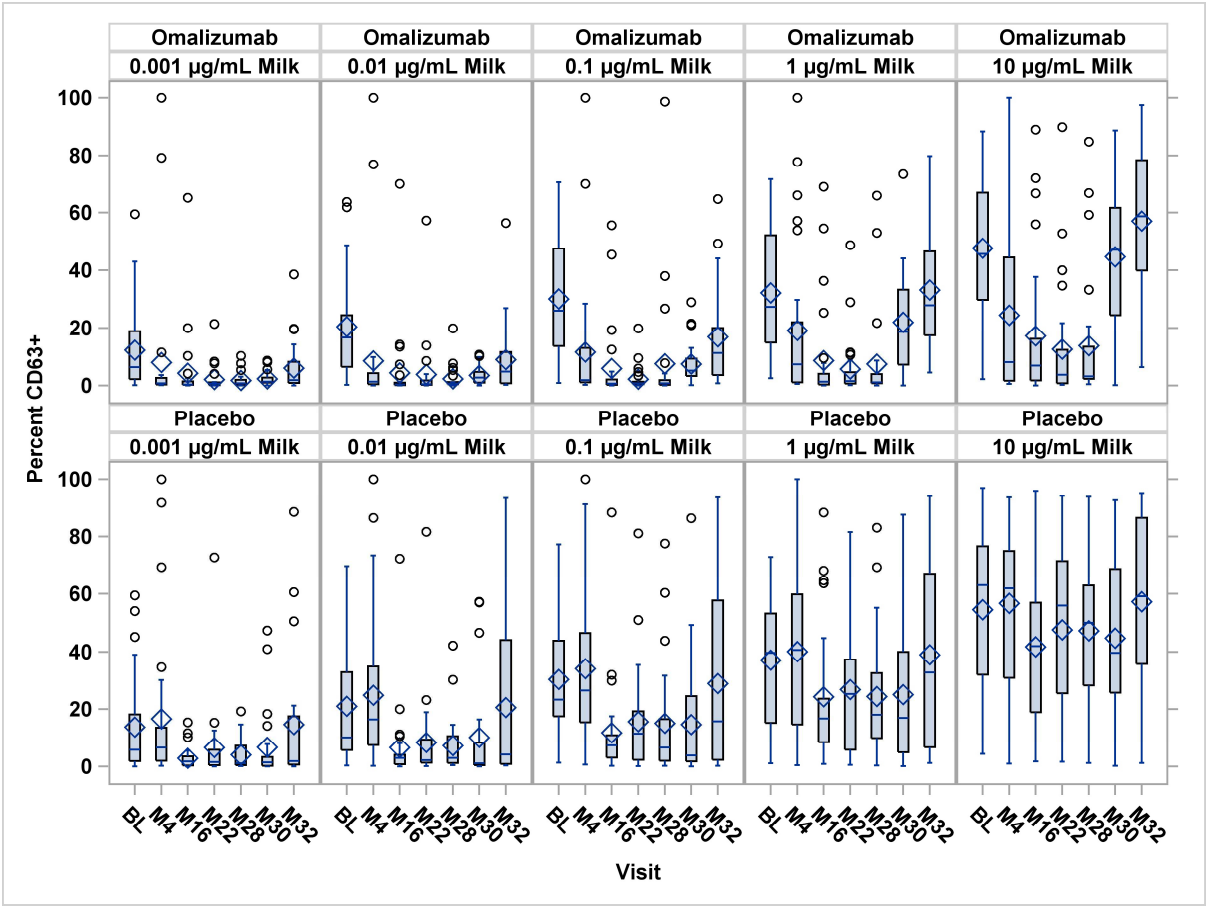
Omalizumab
0.001 µg/mL Milk
Omalizumab
0.01 µg/mL Milk
Omalizumab
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Omalizumab
1 µg/mL Milk
Omalizumab
10 µg/mL Milk
Placebo
0.001 µg/mL Milk
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0.01 µg/mL Milk
Placebo
0.1 µg/mL Milk
Placebo
1 µg/mL Milk
Placebo
10 µg/mL Milk
Percent CD63+
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20
40
60
80
100
BL
M4
M16
M22
M28
M30
M32
Visit