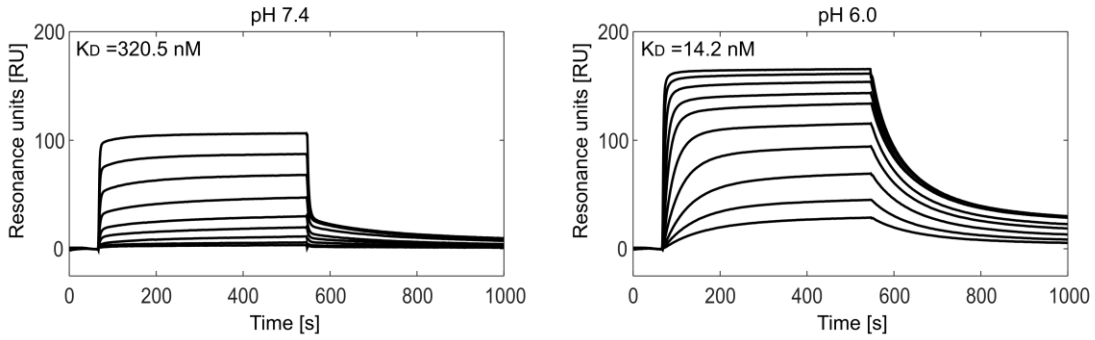
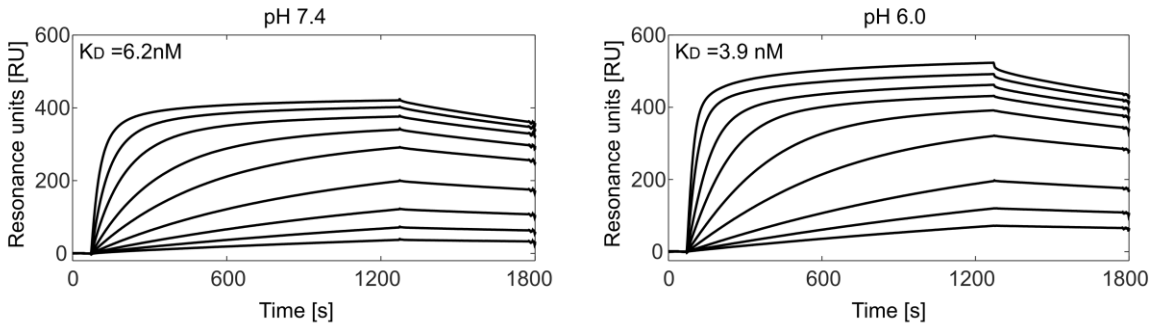
SUPPLEMENTARY DATA

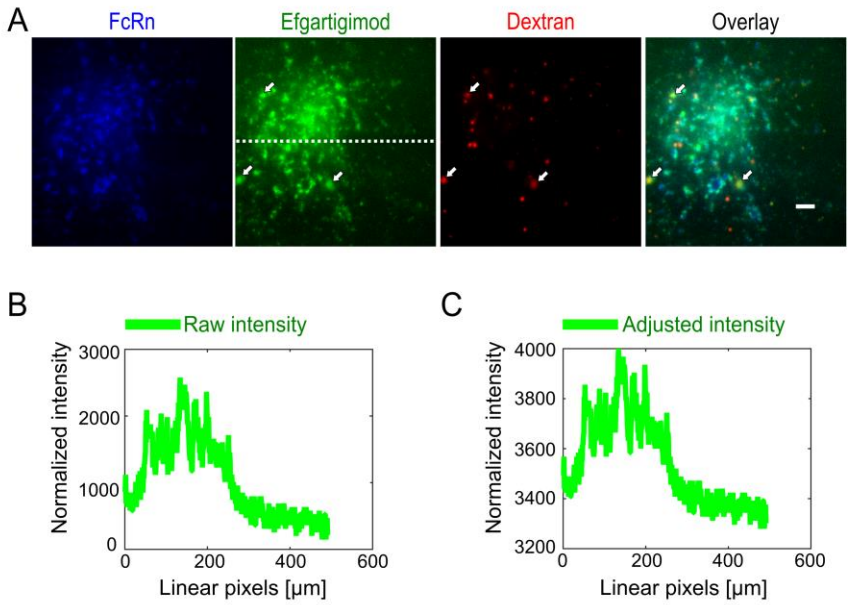
Supplementary Figure 1: Equilibrium binding analyses of the interaction of efgartigimod with human FcRn using SPR. The coupling density of efgartigimod was 275 RU. Human FcRn was injected over the flow cells at concentrations ranging from 0.01-1.33 mM (pH 6.0) or 0.01-2.67 mM (pH 7.4) in PBS (pH 6.0 or pH 7.4), 0.05% Tween at a flow rate of 10 ml/min. Representative sensorgrams for duplicate or triplicate injections for each concentration are shown. Sensorgrams were zero-adjusted and reference cell data subtracted.



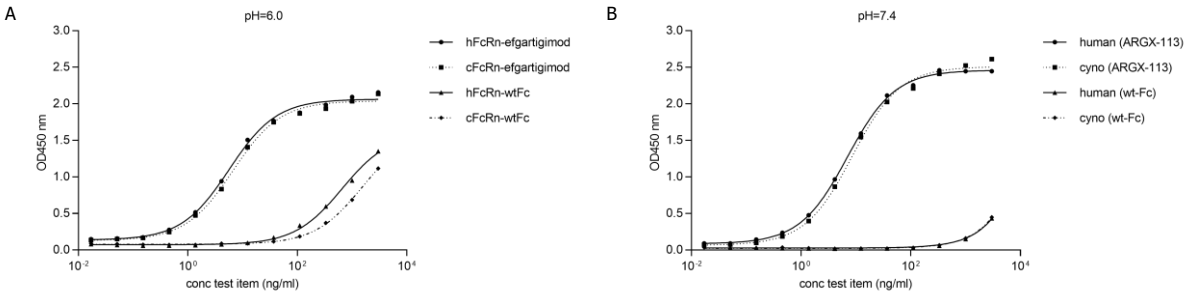
Supplementary Figure 2: **Equilibrium binding analyses of the interaction of the anti-FcRn antibody with human FcRn using SPR**. The coupling density of anti-FcRn antibody was 1552 RU. Human FcRn was injected over the flow cells at concentrations ranging from 0.7-178 (pH 6.0) or 0.7-178 nM (pH 7.4) in PBS (pH 6.0 or pH 7.4), 0.05% Tween at a flow rate of 5 ml/min. Representative sensorgrams for duplicate or triplicate injections for each concentration are shown. Sensorgrams were zero-adjusted and reference cell data subtracted.



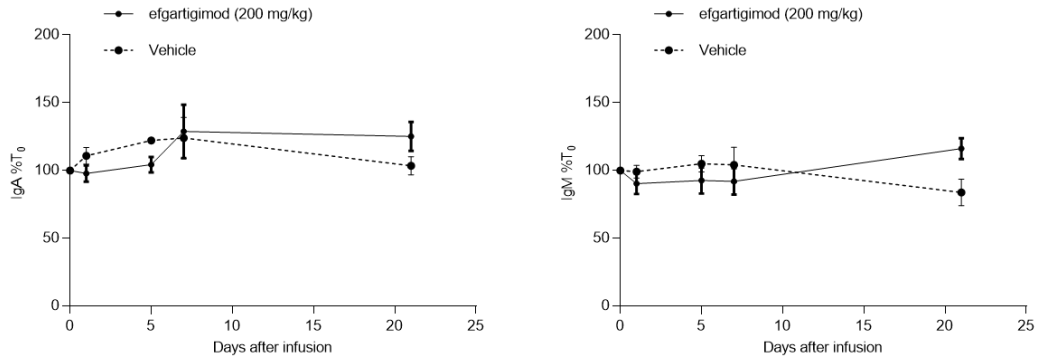
Supplementary Figure 3: **Subcellular trafficking behavior of efgartigimod.** HMEC-1 cells expressing human FcRn-GFP were pulse-chased with 500 µg/ml Alexa 555-labeled dextran to label lysosomes, and then pulse-chased (30 minutes pulse, 16 hours chase) with Alexa 647-labeled efgartigimod (25 µg/ml). A, the intensity of the Alexa 647 channel was piecewise linearly adjusted. White arrowheads in the images indicate the localization of efgartigimod in dextran-positive lysosomes. GFP, Alexa 555, and Alexa 647 are pseudocolored blue, red, and green, respectively. Bar = 3 µm. B,C, pixel intensities for the Alexa 647 fluorescence across the indicated line on the efgartigimod image without any adjustment (B; 'raw' intensity, used for data shown in Figure 2C), or with piecewise linear adjustment (C) for the image shown in A. Consistent with the piecewise linear adjustment of the image shown in A, the pixel traces have the same profiles but the intensities are piecewise linearly offset from each other.



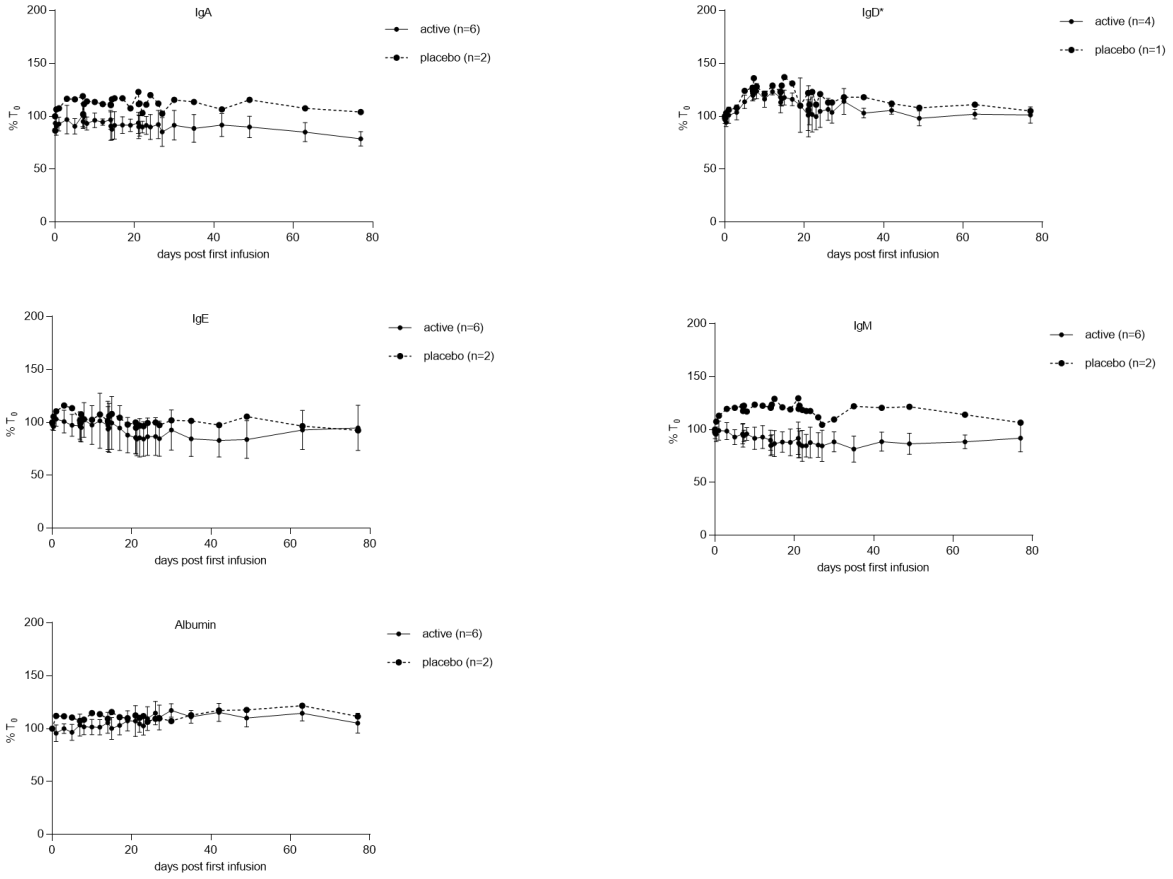
Supplementary Figure 4: Cross-species FcRn binding. Binding of efgartigimod or an unmodified Fc fragment (wt-Fc) to human or cynomolgus monkey FcRn binding at both acidic (A) and neutral pH (B) as measured by ELISA. Representative data for at least 3 experiments are shown.



Supplementary Figure 5: Efgartigimod does not alter IgA nor IgM levels in cynomolgus monkeys. Animals (n = 2/group) were injected with 1 mg/kg of the non-target-binding human IgG1 tracer antibody FR70-hIgG1, followed 2 days later with an i.v. infusion of 200 mg/kg efgartigimod or vehicle. cIgA (A) and cIgM (B) levels in serum, determined using a commercial ELISA kit, were plotted relative to pre-dose levels (percent change from baseline; $\%T_0$). Values are mean ± S.E.M.



Supplementary Figure 6: Serum levels of IgA, IgD, IgE, IgM, and albumin over time in the MAD part of the first-in-human study. Healthy subjects (n = 8) were dosed with 25 mg/kg efgartigimod or placebo q7d on four occasions (Cohort 10). efgartigimod or placebo (randomized in a 6:2 ratio) was administered i.v. in a 2-hour infusion. Percent change versus baseline in IgA, IgD, IgE, IgM, and albumin serum concentration (%T_0) is shown; values are mean ± SD.



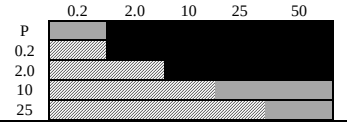
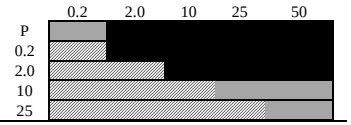
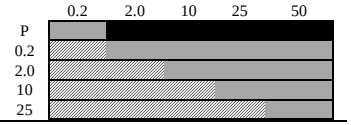
* Two subjects in the active group and 1 subject in the placebo group had IgD values below limit of quantification during the whole study period.

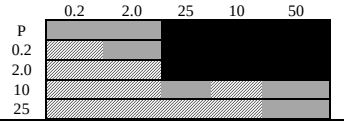
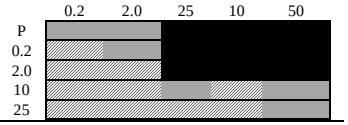
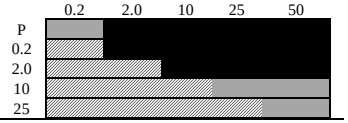
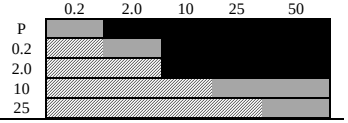
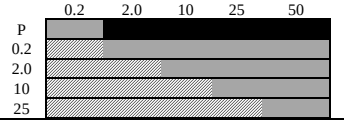
Supplementary Table 1: Mean fluorescence intensity values for flow cytometry experiments. Mean fluorescence intensities (MFIs, Duplicate values for each time point) obtained from two flow cytometric analyses of cell-associated fluorescence for HMEC-1 cells following pulse-chase treatment with fluorescently labeled antibodies/antibody Fc fragments.

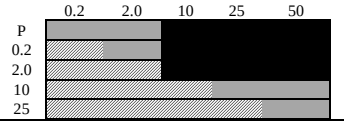
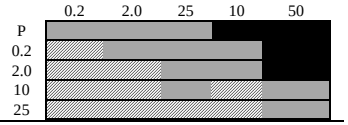
	Chase time	**Experiment 1 (MFI)***		**Experiment 2 (MFI)***	
Efgartigimod	0’	9.4×10^5	8.2×10^5	1.5×10^6	1.4×10^6
	30’	4.3×10^5	3.6×10^5	4.6×10^5	5.0×10^5
	120’	2.4×10^5	2.1×10^5	2.0×10^5	2.2×10^5
Human IgG1	0’	3.4×10^4	2.2×10^4	3.4×10^4	2.7×10^4
	30’	5.5×10^3	7.4×10^3	7.1×10^3	5.4×10^3
	120’	7.4×10^3	4.7×10^3	5.1×10^3	6.2×10^3
Anti-FcRn	0’	1.3×10^6	1.2×10^6	1.9×10^6	2.0×10^6
	30’	1.2×10^6	1.3×10^6	1.9×10^6	1.9×10^6
	120’	1.5×10^6	1.4×10^6	1.7×10^6	1.7×10^6

*Duplicate values for each time point.

Supplementary Table 2: Summary efgartigimod PD parameters (SAD part of the first-in-human study). Healthy subjects (n = 6/group) were dosed with 0.2, 2, 10, 25, or 50 mg/kg efgartigimod or placebo (i.e., Cohort 1-5). efgartigimod or placebo (randomized in a 4:2 ratio) was administered i.v. in a 2-hour infusion. Values are arithmetic mean except median (min-max) for t_{Emax}. AUEC and E_{max} were compared between the treatment groups (placebo subjects pooled) using a one-way ANOVA model with treatment as fixed effect. In case of a significant treatment effect ($p< 0.05$), pairwise comparison between treatments was performed using Tukey's test. For t_{Emax} comparison between treatment groups was assessed by using a non-parametric Kruskal-Wallis test and, in case statistically significant ($p< 0.05$), by applying Wilcoxon's rank sum test with Moses' 90% CIs for pairwise comparisons.

PD Parameter	Pooled Placebo N=10	efgartigimod 0.2 mg/kg N=4	efgartigimod 2.0 mg/kg N=4	efgartigimod 10 mg/kg N=4	efgartigimod 25 mg/kg N=4	efgartigimod 50 mg/kg N=4	ANOVA (p-value) – Tukey's test[a]
IgG1							
E_{max} (%)	-9.77	-7.40	-21.8	-49.1	-54.3	-58.3	<0.0001 
AUEC (%*h)	802	-12.7	-9430	-26900	-29700	-32000	<0.0001 
t_{Emax} (h)	3.0 (2.0-671.7)	120.1 (0.0-504.0)	335.8 (144.0-336.4)	335.8 (332.9-336.0)	335.7 (335.6-336.7)	336.0 (336.0-336.1)	0.0347 

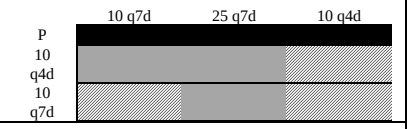
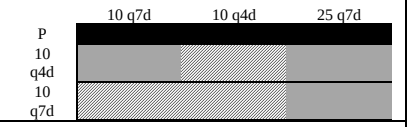
PD Parameter	Pooled Placebo N=10	efgartigimod 0.2 mg/kg N=4	efgartigimod 2.0 mg/kg N=4	efgartigimod 10 mg/kg N=4	efgartigimod 25 mg/kg N=4	efgartigimod 50 mg/kg N=4	ANOVA (p-value) – Tukey's test[a]
IgG2							
E_{max} (%)	-14.2	-13.5	-19.6	-43.5	-42.4	-52.3	<0.0001 
AUEC (%*h)	-1970	-4150	-5390	-23000	-22200	-28400	<0.0001 
t_{Emax} (h)	49.0 (2.0-671.7)	120.1 (4.0-336.0)	216.2 (96.0-336.4)	334.3 (143.9-504.3)	503.9 (503.8-504.1)	504.0 (336.0-504.0)	0.0971
IgG3							
E_{max} (%)	-8.35	-6.25	-24.0	-54.0	-56.2	-61.1	<0.0001 
AUEC (%*h)	3012	1658	-7970	-26900	-27600	-32100	<0.0001 
t_{Emax} (h)	2.0 (0.0-143.7)	120.1 (0.0-504.0)	120.0 (96.0-144.0)	143.8 (96.0-144.1)	144.0 (96.1-335.6)	144.2 (144.0-336.1)	0.0004 

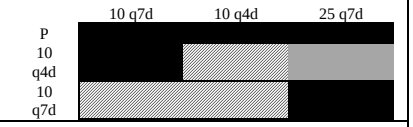
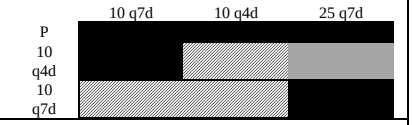
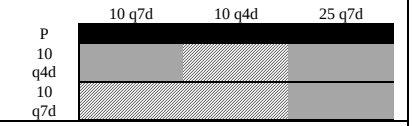
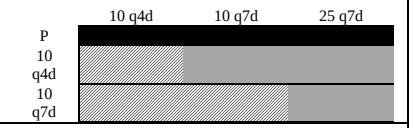
PD Parameter	Pooled Placebo N=10	efgartigimod 0.2 mg/kg N=4	efgartigimod 2.0 mg/kg N=4	efgartigimod 10 mg/kg N=4	efgartigimod 25 mg/kg N=4	efgartigimod 50 mg/kg N=4	ANOVA (p-value) – Tukey's test[a]
IgG4							
E_{max} (%)	-10.5	-9.92	-16.1	-36.6	-42.3	-46.0	<0.0001 
AUEC (%*h)	812	-1160	-5730	-18900	-12200	-25000	0.0001 
t_{Emax} (h)	4.0 (2.0-671.7)	144.1 (4.0-504.0)	335.8 (144.0-336.4)	238.4 (143.8-335.9)	335.6 (72.1-504.1)	336.0 (336.0-336.1)	0.2453

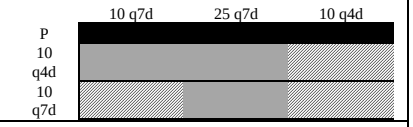
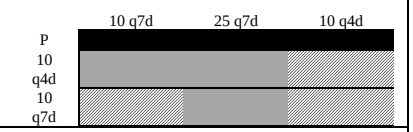
N, number of subjects.

[a] Tukey's test: means are sorted in descending order, black: doses statistically different, gray: doses not statistically different; Kruskal-Wallis and Wilcoxon's rank sum test for tEmax

Supplementary Table 3: Summary efgartigimod PD parameters (MAD part of the first-in-human study). Healthy subjects (n = 8/group) were dosed with 10 mg/kg efgartigimod or placebo q4d on six occasions (Cohort 7), 10 mg/kg efgartigimod or placebo q7d on four occasions (Cohort 9), or 25 mg/kg efgartigimod or placebo q7d on four occasions (Cohort 10). efgartigimod or placebo (randomized in a 6:2 ratio) was administered i.v. in a 2-hour infusion. Values are arithmetic mean except median (min-max) for t_{Emax}. AUEC and E_{max} were compared between the treatment groups (placebo subjects pooled) using a one-way ANOVA model with treatment as fixed effect. In case of a significant treatment effect ($p< 0.05$), pairwise comparison between treatments was performed using Tukey's test. For t_{Emax} comparison between treatment groups was assessed by using a non-parametric Kruskal-Wallis test and, in case statistically significant ($p< 0.05$), by applying Wilcoxon's rank sum test with Moses' 90% CIs for pairwise comparisons.

PD Parameter	Pooled Placebo N=6	efgartigimod 10 mg/kg q4d N=5	efgartigimod 10 mg/kg q7d N=6	efgartigimod 25 mg/kg q7d[a] N=6	ANOVA (p-value) – Tukey's test[b]
IgG1					
E_{max} (%)	-8.32	-78.5	-73.0	-77.7	<0.0001 
AUEC (%*h)	15502	-75700	-65100	-91700	<0.0001 
t_{Emax} (h)	302.0 (0.0-1824)	576.0 (482.0-696.0)	576.0 (552.0-648.2)	624.2 (456.0-648.6)	0.3713

PD Parameter	Pooled Placebo N=6	efgartigimod 10 mg/kg q4d N=5	efgartigimod 10 mg/kg q7d N=6	efgartigimod 25 mg/kg q7d[a] N=6	ANOVA (p-value) – Tukey's test[b]
IgG2					
E_{max} (%)	-8.58	-74.9	-64.6	-76.8	<0.0001 
AUEC (%*h)	24450	-85200	-56800	-101000	<0.0001 
t_{Emax} (h)	97.0 (0.0-1849)	576.0 (482.0-624.0)	576.0 (408.0-648.2)	624.5 (576.0-648.5)	0.0802
IgG3					
E_{max} (%)	-11.3	-77.6	-73.3	-77.9	<0.0001 
AUEC (%*h)	18730	-59600	-62500	-78800	<0.0001 
t_{Emax} (h)	312.0 (0.0-839.8)	432.0 (336.0-488.0)	552.0 (408.0-624.0)	480.0 (360.0-648.6)	0.3219

PD Parameter	Pooled Placebo N=6	efgartigimod 10 mg/kg q4d N=5	efgartigimod 10 mg/kg q7d N=6	efgartigimod 25 mg/kg q7d[a] N=6	ANOVA (p-value) – Tukey's test[b]
			IgG4		
E_{max} (%)	-8.81	-66.6	-58.1	-62.3	<0.0001 
AUEC (%*h)	9895	-60200	-47400	-56300	<0.0001 
t_{Emax} (h)	277.0 (0.0-648.1)	576.0 (482.0-696.0)	576.0 (528.0-648.2)	564.0 (360.0-648.6)	0.4514

N, number of subjects.

[a] For the q7d regimen at the dose 25 mg/kg, only the data from the Cohort 10 are summarized in this table

[b] Tukey's test: means are sorted in descending order, black: doses statistically different, gray: doses not statistically different; Kruskal-Wallis test for t_{Emax}

Supplementary Table 4: Demographic Data and Baseline Characteristics – SAD Part

Parameter	Placebo N=10	efgartigimod 0.2 mg/kg N=4	efgartigimod 2.0 mg/kg N=4	efgartigimod 10 mg/kg N=4	efgartigimod 25 mg/kg N=4	efgartigimod 50 mg/kg N=4	All subjects N=30
Age, years	39.5	46.5	44.0	51.5	50.0	44.5	46.5
Median (range)	(22-51)	(39-50)	(36-51)	(50-53)	(35-55)	(40-54)	(22-55)
Height, cm	176.00	180.15	178.05	171.95	182.50	177.50	177.50
Median (range)	(157.0-189.0)	(155.2-186.0)	(163.0-185.0)	(165.5-178.0)	(165.5-192.0)	(173.0-184.0)	(155.2-192.0)
Weight, kg	73.60	77.30	74.10	80.90	75.00	76.70	75.20
Median (range)	(54.8-98.6)	(55.8-87.6)	(54.8-81.2)	(78.2-82.0)	(72.8-86.8)	(62.8-87.0)	(54.8-98.6)
BMI, kg/m^2	23.85	23.85	23.10	26.95	23.55	24.30	24.00
Median (range)	(19.7-30.4*)	(21.7-26.9)	(20.6-24.3)	(25.4-29.9)	(21.5-26.6)	(21.0-25.7)	(19.7-30.4)
Race, n (%)							
White	10 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	30 (100)
Ethnicity, n (%)							
Not Hispanic or Latino	10 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	30 (100)
Gender, n (%)							
Female	3 (30.0)	1 (25.0)	0	0	0	0	4 (13.3)
Male	7 (70.0)	3 (75.0)	4 (100)	4 (100)	4 (100)	4 (100)	26 (86.7)

N=number of subjects; n=number of subjects with that observation

* The BMI of 30.4 kg/m^2 was determined at Day -1. The BMI at screening for this subject was 29.6 kg/m^2.

Supplementary Table 5: Demographic Data and Baseline Characteristics – MAD Part (q4d regimen)

Parameter	Placebo N=2	efgartigimod 10 mg/kg (q4d) N=6	All subjects N=8
Age, years			
Median (range)	34.5 (30-39)	45.5 (18-53)	42.0 (18-53)
Height, cm			
Median (range)	180.45 (177.5-183.4)	172.60 (165.8-187.0)	175.35 (165.8-187.0)
Weight, kg			
Median (range)	82.20 (68.2-96.2)	76.90 (65.0-84.4)	76.90 (65.0-96.2)
BMI, kg/m^2			
Median (range)	25.10 (21.6-28.6)	24.80 (21.7-27.9)	24.80 (21.6-28.6)
Race, n (%)			
Asian	0	2 (33.3)	2 (25.0)
White	2 (100)	4 (66.7)	6 (75.0)
Ethnicity, n (%)			
Hispanic or Latino	0	1 (16.7)	1 (12.5)
Not Hispanic or Latino	2 (100)	5 (83.3)	7 (87.5)
Gender, n (%)			
Male	2 (100)	6 (100)	8 (100)

N=number of subjects; n=number of subjects with that observation

Supplementary Table 6: Demographic Data and Baseline Characteristics – MAD Part (q7d regimen)

Parameter	Placebo N=6	efgartigimod 25 mg/kg q7d (Cohort 8) * N=6	efgartigimod 10 mg/kg q7d (Cohort 9) N=6	efgartigimod 25 mg/kg q7d (Cohort 10) N=6	All subjects N=24
Age, years					
Median (range)	38.5 (22-53)	48.5 (40-55)	47.0 (38-53)	44.5 (33-55)	46.5 (22-55)
Height, cm					
Median (range)	182.05 (177.0-192.8)	179.25 (169.0-183.6)	178.75 (168.4-182.8)	178.35 (170.1-183.0)	179.30 (168.4-192.8)
Weight, kg					
Median (range)	89.10 (66.6-97.0)	85.40 (62.0-93.0)	79.10 (67.2-93.4)	77.35 (73.0-85.6)	82.50 (62.0-97.0)
BMI, kg/m^2					
Median (range)	26.20 (21.3-28.9)	26.90 (21.7-29.7)	26.15 (23.2-29.0)	24.50 (23.8-27.1)	25.85 (21.3-29.7)
Race, n (%)					
Asian	0	0	2 (33.3)	0	2 (8.3)
Black or African American	0	0	0	1 (16.7)	1 (4.2)
White	6 (100)	6 (100)	4 (66.7)	5 (83.3)	21 (87.5)
Ethnicity, n (%)					
Not reported**	0	0	1	0	1
Not Hispanic or Latino	6 (100)	6 (100)	5 (100)	6 (100)	23 (100)
Gender, n (%)					
Male	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)

N=number of subjects; n=number of subjects with that observation

* Subjects in cohort 8 were dosed with either 1 dose (n=1 with placebo and n=3 with efgartigimod) or 2 doses (n=1 with placebo and n=3 with efgartigimod) only.

** 'Not reported' values were excluded from the denominator for the percentage calculation.