SUPPLEMENTARY MATERIALS

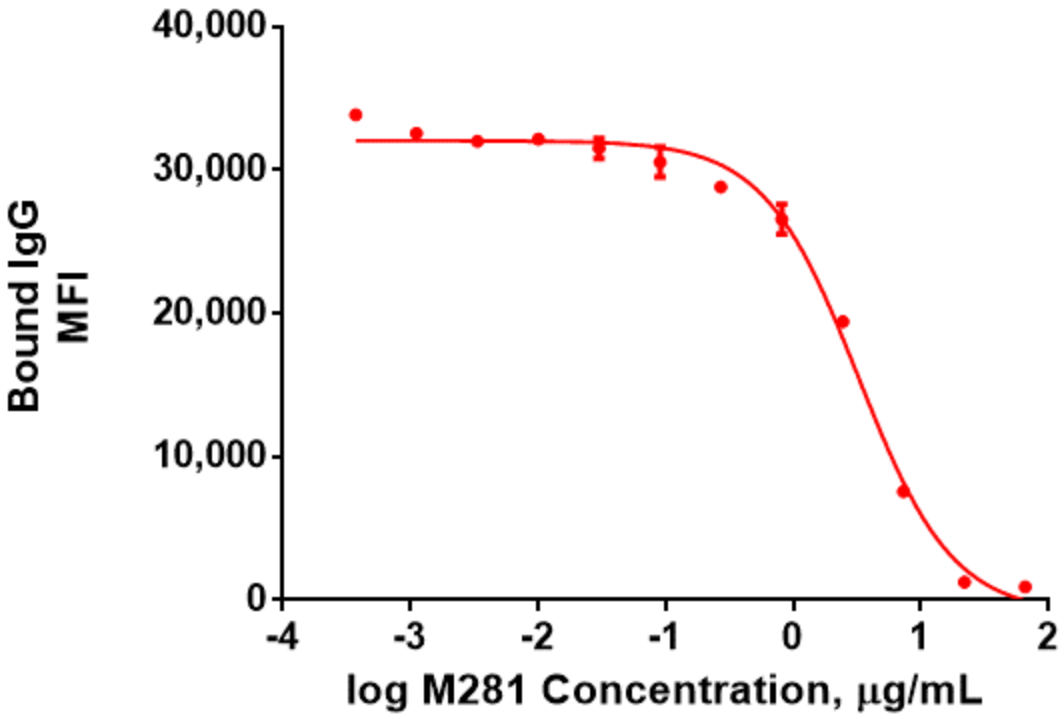
Table S1 Binding affinity of M281 to human FcRn at pH 7.6 and 6.0

	ka1, $M^{-1}sec^{-1}$	kd1, sec^{-1}	ka2, sec^{-1}	kd2, sec^{-1}	KD, pM
pH 7.6	1.04E+06	2.12E-03	7.86E-03	9.10E-04	43.5

	Ka, $M^{-1}sec^{-1}$	kd, sec^{-1}	KD, pM
pH 6.0	1.63E+06	4.53E-05	28.7

The affinity of M281 interaction with human neonatal Fc receptor (FcRn) in the absence of avidity was determined by surface plasmon resonance binding kinetics on a Biacore T200 (GE Healthcare Life Sciences, Marlborough, Massachusetts) at 25^{o}C. In testing conducted in HBS-P at pH7.6 an anti-Human immunoglobulin (IgG) antibody was immobilized by amine coupling on the sensor surface and was used to capture M281. Binding of solution phase recombinant human FcRn extracellular domain was measured, and the double-reference subtracted kinetic data were fit to a two-state reaction model to accurately represent the binding mode of M281 to FcRn. In testing conducted in PBS-T at pH 6.0, M281 was directly immobilized on the sensor surface using amine coupling. Binding of solution-phase FcRn was monitored, and double-reference subtracted sensor grams were fit to a 1:1 binding model to estimate kinetic and equilibrium binding constants.

Figure S1. Inhibition of IgG binding to FcRn by M281.



	M281
log(agonist) vs. response -- Variable slope (four parameters)	
Best-fit values	
Bottom	-972.2
Top	32034
LogEC50	0.5117
HillSlope	-1.176
EC50	3.248
Span	33006

IgG competition binding assays were performed at pH 6.0 to mimic endosomal conditions and assessed the binding of Dylight-650 labeled IgG (anti-FITC IgG1 monoclonal antibody) to human FcRn extracellular domain expressed at the cell surface of HEK 293 cells in suspension. Human FcRn extracellular domain fused to rat thy1 GPI was transiently expressed in HEK293

cells (AnaptysBio, San Diego) and a stable, high-expressing pool of cells selected and cryopreserved for all studies. Cells were thawed and cultured in Freestyle media + G418. Cells prepared for assay were washed and resuspended in pH 6.0 binding buffer (PBS, 25 mM HEPES, 10 mM EDTA, 1% glucose, adjusted to pH 6.0 with citric acid). Cells (2.5×10^5) were incubated with DyL650-IgG1 (66 nM) premixed with 2-fold dilutions of anti-FcRn antibody for 30 minutes on ice. Cells were washed with pH 6.0 binding buffer, resuspended in 1% paraformaldehyde for 10 minutes, centrifuged, washed on ice and resuspended in pH 6.0 binding buffer. Samples were analyzed for fluorescence on a BD Verse flow cytometer for fluorescence-activated cell sorting. Mean fluorescence intensity (MFI) values of the ungated cell population are graphed.

Table S2 E_{max} and T_{max} for total IgG and IgG subclass by dose group

			Maximal IgG decline from baseline								
			Single-dose cohorts						Multiple-dose cohorts*		
Parameter			0.3 mg/kg (n = 3)	3 mg/kg (n = 3)	10 mg/kg (n = 6)	30 mg/kg (n = 6)	60 mg/kg (n = 6)	Placebo (n = 10)	30 mg/kg (n = 6)	15 mg/kg (n = 6)	Placebo (n = 4)
Total IgG	E_{max}	Mean, %	12	32	56	75	81	9	84	83	3
	T_{Emax}	Median, hr	1	11	7	9	14	1	24	20	28
IgG1	E_{max}	Mean, %	19	41	57	74	81	17	84	84	16
	T_{Emax}	Median, hr	1	11	7	11	14	4	28	20	24
IgG2	E_{max}	Mean, %	17	37	41	57	69	24	82	69	36
	T_{Emax}	Median, hr	3	0.1	9	11	13	4	24	20	30
IgG3	E_{max}	Mean, %	46	58	81	87	91	32	91	91	42
	T_{Emax}	Median, hr	3	3	7	7	14	1	17	17	63
IgG4	E_{max}	Mean, %	29	32	57	64	49	22	79	83	46
	T_{Emax}	Median, hr	3	3	7	9	14	1	20	28	81

E_{max}, maximum percent reduction from baseline; IgG, immunoglobulin G; T_{Emax}, time to maximum percent reduction.

*All subjects were used to calculate mean E_{max}, regardless of the number of doses received as all subjects reached a maximal IgG plateau as percent of baseline after 2 doses.

The mean of an individual subject's maximum IgG or IgG subclasses responses and the median time of occurrence of individual maximum IgG responses were determined. The maximum observed percent reduction (E_{max}) from baseline is the ratio of the minimum observed post-dose serum concentration relative to baseline predose. E_{max} and time to maximum percent reduction (T_{Emax}) values were summarized by subject and descriptive statistics were calculated using R version 3.4.3 (The R Foundation, Vienna, Austria)

Table S3 Mean (SD) serum albumin and total serum protein in subjects (n = 3) receiving 4 consecutive M281 weekly doses.

Parameter	M281 Dose, mg/kg	Time of Assessment After First Dose				
		Baseline*	28 days	42 days	56 days	84 days
Serum albumin, g/L	30	36 (4)	28 (2)	32 (3)	35 (2)	37 (3)
	15	40 (2)	32 (1)	36 (2)	40 (2)	41 (1)
Total serum protein, g/L	30	68 (3)	53 (3)	60 (3)	63 (1)	68 (4)
	15	72 (5)	54 (2)	61 (3)	65 (3)	67 (4)

*Baseline values were obtained 18 hours before the first dose.

Reference ranges: Albumin, 34-50 g/L; total serum protein, 63-85 g/L.