

SUPPLEMENTARY DATA

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Supplementary Table 1. Pre-specified subgroup analyses of change from baseline in C-peptide AUC at Month 12 (ITT population)

Subgroup	Treatment comparison					
	Placebo		Otelixizumab		Difference	p-value
	n	Estimate (SE)*	n	Estimate (SE)	Estimate (95% CI)	
Age						
Adolescent		-0.35 (0.096)		-0.30 (0.071)	0.05 (-0.18, 0.28)	0.662
Adult		-0.21 (0.032)		-0.20 (0.023)	0.01 (-0.07, 0.09)	0.801
Continent						
North America		-0.25 (0.036)		-0.22 (0.026)	0.03 (-0.05, 0.12)	0.439
Europe		-0.19 (0.050)		-0.20 (0.035)	-0.01 (-0.13, 0.11)	0.892
Baseline C-peptide AUC						
Low		-0.03 (0.052)		-0.08 (0.039)	-0.04 (-0.17, 0.09) [†]	0.525
Medium		-0.22 (0.050)		-0.14 (0.035)	0.08 (-0.04, 0.20) [†]	0.185
High		-0.39 (0.054)		-0.41 (0.038)	-0.02 (-0.15, 0.11) [†]	0.732
Baseline insulin use						
Low		-0.23 (0.054)		-0.24 (0.036)	-0.00 (-0.13, 0.12)	0.939
Medium		-0.26 (0.049)		-0.24 (0.037)	0.02 (-0.10, 0.14)	0.788
High		-0.14 (0.054)		-0.12 (0.037)	0.02 (-0.11, 0.14)	0.780
Baseline HbA1c						
Low		-0.26 (0.045)		-0.19 (0.032)	0.07 (-0.04, 0.18) [†]	0.196
Medium		-0.23 (0.053)		-0.20 (0.035)	0.03 (-0.09, 0.16) [†]	0.627
High		-0.15 (0.059)		-0.24 (0.045)	-0.09 (-0.23, 0.06) [†]	0.241
Baseline BMI						
Low		-0.25 (0.054)		-0.22 (0.037)	0.04 (-0.09, 0.16)	0.586
Medium		-0.24 (0.047)		-0.16 (0.037)	0.08 (-0.04, 0.20)	0.177
High		-0.18 (0.053)		-0.23 (0.037)	-0.06 (-0.18, 0.07)	0.363
Gender						
Male		-0.16 (0.036)		-0.18 (0.026)	-0.02 (-0.11, 0.06)	0.616
Female		-0.34 (0.049)		-0.24 (0.035)	0.10 (-0.02, 0.22)	0.103
Anti-GAD status						
Negative		-0.15 (0.104)		-0.09 (0.072)	0.06 (-0.19, 0.31)	0.642
Positive		-0.23 (0.031)		-0.21 (0.022)	0.02 (-0.06, 0.09)	0.687
Anti-IA2 status						
Negative		-0.19 (0.060)		-0.17 (0.036)	0.02 (-0.12, 0.16) [†]	0.774
Positive		-0.23 (0.034)		-0.22 (0.026)	0.01 (-0.07, 0.10) [†]	0.752

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Number of positive autoantibody results						
One (GAD or IA-2)		-0.21 (0.060)		-0.19 (0.032)	0.02 (-0.11, 0.16)	0.742
Two (GAD and IA-2)		-0.23 (0.034)		-0.22 (0.027)	0.01 (-0.08, 0.09)	0.826

*nmol/L; †Estimated treatment group difference within a subgroup, adjusted for age, region and baseline C-peptide AUC. AUC = area under the curve; BMI = body mass index; CI = confidence interval, not adjusted for multiple comparisons; GAD = glutamic acid decarboxylase; IA = insulin antibody.

Supplementary Table 2. Secondary efficacy parameters at Month 12 (ITT population)

Parameter	Observed mean				Model based*		p-value†
	Placebo n = 91		Otelixizumab n = 181		Placebo	Otelixizumab	
	n	Estimate (SE)	n	Estimate (SE)	Estimate (SE)	Estimate (SE)	
Change from baseline mean daily insulin use, IU/kg	77	0.07 (0.028)	167	0.03 (0.018)	0.07 (0.023)	0.04 (0.016)	0.277
Mean daily insulin use, IU/kg	81	0.43 (0.026)	169	0.39 (0.017)	0.42 (0.024)	0.39 (0.017)	0.276
Change from baseline HbA1c, %	82	-0.39 (0.174)	162	-0.15 (0.117)	-0.38 (0.140)	-0.20 (0.101)	0.304
HbA1c, %	82	6.91 (0.147)	162	7.04 (0.116)	6.83 (0.146)	7.02 (0.108)	0.289
Change from baseline IDAA1c	86	-0.07 (0.213)	176	0.03 (0.157)	-0.15 (0.197)	-0.02 (0.139)	0.584
IDAA1c	90	8.58 (0.194)	178	8.72 (0.171)	8.49 (0.203)	8.64 (0.149)	0.526
Change from baseline ADRR	59	3.41 (1.292)	121	4.42 (0.759)	3.29 (1.037)	4.22 (0.732)	0.463
ADRR	66	18.09 (1.263)	142	19.08 (0.881)	18.26 (1.075)	19.02 (0.787)	0.535
Glycemic excursions‡	78		161		-	-	
Number		2.9 (0.41)		3.2 (0.32)			
Maximum value of excursion, mg/dL		11.2 (1.20)		11.0 (0.92)			

*Estimates based on model least squares mean. Mixed-effects repeated measures models adjust for age, continent and baseline parameter. †p-value for treatment comparison based on model. Month 12 p-value is unadjusted. ‡≤ 70 mg/dL. ADRR = average daily risk range; IDACC = insulin dose-adjusted HbA1c; ITT = intent to treat.

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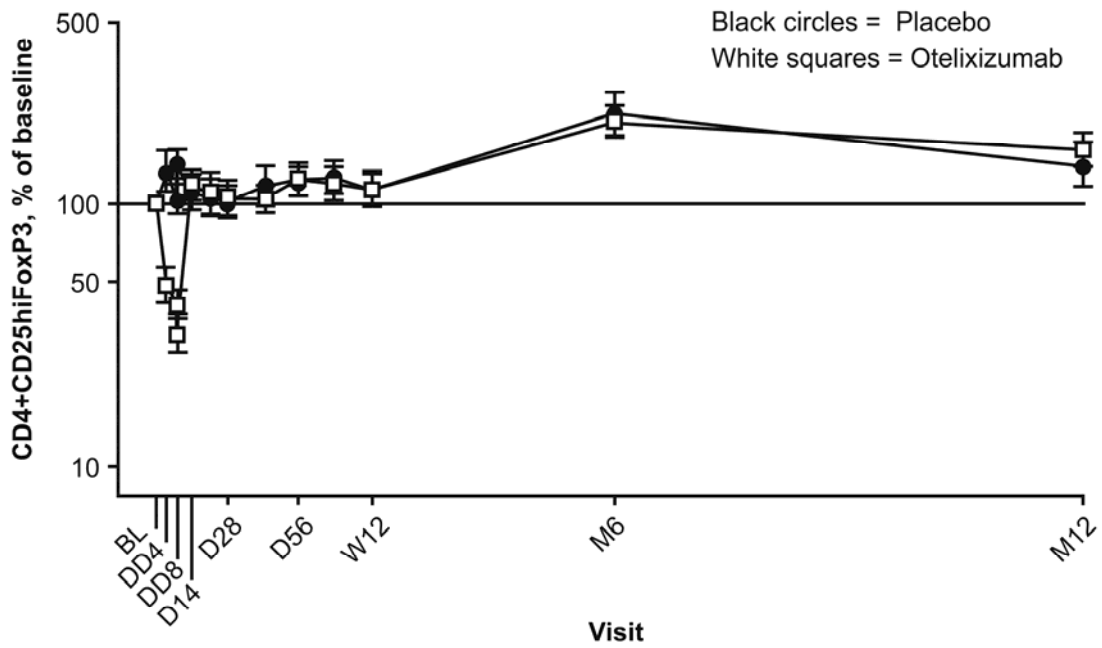
Supplementary Table 3. Adverse events by group in DEFEND

Event, n (%)	Overall	
	Otelixizumab n = 181	Placebo n = 91
Headache	155 (85.6)	45 (49.5)
Nausea	60 (33.1)	20 (22.0)
Vomiting	35 (19.3)	13 (14.3)
Pyrexia	34 (18.8)	10 (11.0)
Chills	24 (13.3)	6 (6.6)
Hypoglycemia	23 (12.7)	8 (8.8)
Overall number of severe episodes (%)	4 (2.2)	2 (2.2)
Overall number of symptomatic episodes (%)	163 (90.1)	78 (85.7)
Overall number of asymptomatic episodes (%)	13 (7.2)	10 (11.0)
Myalgia	21 (11.6)	14 (15.4)
Arthralgia	20 (11.0)	2 (2.2)
Infections and infestations	2 (1.1)	4 (4.4)

*Severe hypoglycemia: requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions; documented symptomatic hypoglycemia: typical symptoms of hypoglycemia accompanied by a measured plasma glucose (PG) \leq 3.9 mmol/L; asymptomatic hypoglycemia: not accompanied by typical symptoms of hypoglycemia but with a measured PG \leq 3.9 mmol/L.(19,20)

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Supplementary Figure 1. Change in CD4+CD25^{hi}FoxP3⁺ T cells over time in both groups



BL = baseline; D = day; DD = dosing day; M = month; W = week