The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: OTX115495 (formerly TRX4006)
Title: DEFEND-1: Durable-Response Therapy Evaluation for Early- or New-Onset Type 1 Diabetes
Rationale: Otelixizumab is an anti-human CD3 monoclonal antibody (mAb) directed against the epsilon domain of the human lymphocyte antigen CD3. Type 1 diabetes mellitus (T1DM) is an autoimmune disorder that is characterized by a progressive loss in β cell functionality. T cells play a predominant role in this inflammatory response. There are no available therapies able to preserve β cell function in subjects with T1DM. This study was designed to measure the effect of otelixizumab on preservation of β cell function in subjects with T1DM.
Phase: III
Study Period to Month 24: 29 July 2008-31 January 2012
Study Design: A randomized, placebo-controlled, double-blind, multicenter study of the efficacy and safety of otelixizumab in approximately 240 adolescents and adults with new-onset type 1 diabetes mellitus (NOT1DM). The study consisted of a screening phase of up to 35 days, an 8 day dosing period and a short (up to Month 12) and long-term (up to Month 24) follow-up period. Data to Month 24 are presented here.
Centres: 85 centres in 9 countries: Canada (4), Germany (3), Denmark (1), Spain (5), Finland (2), United Kingdom (4), Italy (8), Sweden (11), and United States of America (47).
Indication: Type 1 diabetes mellitus
Treatment: Otelixizumab or matching placebo was diluted in 0.9% saline solution for intravenous (IV) infusion over 30 minutes or 2 hours on Days 1-8 of the study. A total of 3.1 mg of otelixizumab was administered over 8 days at 0.1 mg on Day 1, 0.2 mg on Day 2, 0.3 mg on Day 3, and 0.5 mg per day on Days 4-8. The infusion period was reduced from 2 hours to 30 minutes in an amendment to the protocol. At the time of the amendment approximately 60% of subjects in each treatment group had been infused with study drug for 2 hours.
Objectives: The primary objective was to demonstrate that subjects who receive an 8-day series of otelixizumab infusions have greater improvement than subjects who receive placebo in endogenous insulin secretion, as assessed by area under the concentration-time curve (AUC) for mixed meal-stimulated C-peptide, at 12 months after study drug administration.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was change from baseline in 2-hour mixed meal-stimulated C-peptide AUC (normalized for 120-minute time interval) at Month 12
Secondary Outcome/Efficacy Variable(s): Key secondary endpoints were: responder status (where a responder was defined as a subject with HbA1c ≤6.5% and a mean daily insulin use over 7 consecutive days <0.5 IU/kg/day during the 2 weeks prior to the assessment), mean daily insulin use over 7 consecutive days during the 2 weeks prior to the assessment; and HbA1c levels. Other secondary endpoints were incidence of hypoglycaemia; hypoglycaemic and hyperglycaemic excursions; average Daily Risk Ratio (ADRR); baseline-adjusted HbA1c and exogenous insulin use; baseline adjusted C-peptide AUC, HbA1c, and exogenous insulin use; HbA1c and mean daily insulin use over time; subject C-peptide AUC and mean daily insulin use over time; HbA1c and C-peptide AUC. Pharmacodynamic endpoints were absolute counts and percentages of lymphocyte subsets, cell-bound otelixizumab, CD3/T cell receptor (TCR) saturation and modulation, and serum levels of cytokines and cellular mediators.
Statistical Methods: A sample size of 180 subjects (120 in the otelixizumab and 60 in the placebo group) provided 90% power to detect a treatment effect of 0.22 nmol/L on the primary endpoint in a two-sided t-test (α=0.05). The planned sample size was 240 subjects assuming a drop-out rate of 25%. The efficacy (Intent-to-Treat) and safety populations consisted of all subjects who received any part of at least 1 infusion of study drug. The primary efficacy endpoint was analyzed using a repeated-measures mixed-effects model with change from baseline C-peptide AUC, age group, continent, treatment group, visit, and treatment group-by-visit interaction as independent variables. The treatment difference was significant if the two-sided p value was ≤0.05. Responders were compared by 1-sided tests of equality based on the normal approximation to the binomial distribution; Hochberg-adjusted p-values were reported. Exogenous insulin use and HbA1c endpoints were compared using the same repeated-measures mixed-effects model as the primary endpoint. The composite outcomes HbA1c/exogenous insulin use, and C-peptide AUC/HbA1c/exogenous insulin use were compared between treatments using the O'Brien nonparametric ranks test procedure; p-values were Hochberg corrected.
Study Population:

	Placebo	Otelixizumab

Number of Subjects:		
Planned, N	80	160
Randomised, N	91	181
Completed, n (%)	68 (74.7)	152 (84.0)
Total Number Subjects Withdrawn, N (%)	23 (25.3)	29 (16.0)
Withdrawn due to Adverse Events n (%)	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	23 (25.3)	29 (16.0)
Demographics	Placebo	Otelixizumab
N (ITT)	91	181
Females: Males	31:60	64:117
Mean Age, years (SD)	25.2 (7.13)	24.7 (6.54)
White, n (%)	85 (93.4)	169 (93.4)
N adolescents randomized	10	19
Adolescents Mean Age, years (SD)	14.3 (1.77)	13.7 (1.80)
Primary Efficacy Results:		
Change from baseline C-peptide AUC (nmol/L) at Month 12	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.21 (0.030)	-0.21 (0.021)
Difference between treatments	0.01	
95% Confidence Interval	(-0.06, 0.08)	
p-value	0.813	
Secondary Outcome Variable(s):		
C-peptide AUC (nmol/L) at Month 12	Placebo	Otelixizumab
Mean (SE) at Month 12	0.50 (0.034)	0.51 (0.027)
Difference between treatments	0.01	
95% CI	(-0.06, 0.08)	
Change from baseline C-peptide AUC (nmol/L) at Month 6	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.12 (0.028)	-0.09 (0.020)
Difference between treatments	0.03	
95% Confidence Interval	(-0.04, 0.10)	
C-peptide AUC (nmol/L) at Month 6	Placebo	Otelixizumab
Mean (SE) at Month 6	0.60 (0.034)	0.63 (0.027)
Difference between treatments	0.03	
95% CI	(-0.04, 0.10)	
Change from baseline C-peptide AUC (nmol/L) at Month 3	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.04 (0.028)	-0.05 (0.020)
Difference between treatments	-0.01	
95% Confidence Interval	(-0.08, 0.06)	
C-peptide AUC (nmol/L) at Month 3	Placebo	Otelixizumab
Mean (SE) at Month 3	0.69 (0.034)	0.68 (0.027)
Difference between treatments	-0.02	
95% CI	(-0.09, 0.05)	
Change from Baseline Mean Daily Insulin Use (IU/kg) at Month 12	Placebo	Otelixizumab
Mean change from baseline (SE)	0.07 (0.023)	0.04 (0.016)
Difference between treatments	-0.03	
95% Confidence Interval	(-0.08, 0.02)	
Mean Daily Insulin Use at Month 12(IU/kg)	Placebo	Otelixizumab
Mean (SE) at Month 12	0.42 (0.023)	0.39 (0.017)
Difference between treatments	-0.03	
95% Confidence Interval	(-0.08, 0.02)	
Change from Baseline Mean Daily Insulin Use (IU/kg) at Month 6	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.00 (0.021)	-0.00 (0.015)
Difference between treatments	0.00	
95% Confidence Interval	(-0.05, 0.05)	

Mean Daily Insulin Use at Month 6(IU/kg)	Placebo	Otelixizumab
Mean (SE) at Month 6	0.36 (0.022)	0.36 (0.016)
Difference between treatments	0.00	
95% Confidence Interval	(-0.05, 0.05)	
Change from Baseline Mean Daily Insulin Use (IU/kg) at Month 3	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.02 (0.016)	-0.04 (0.011)
Difference between treatments	-0.03	
95% Confidence Interval	(-0.07, 0.01)	
Mean Daily Insulin Use at Month 3(IU/kg)	Placebo	Otelixizumab
Mean (SE) at Month 3	0.34 (0.017)	0.31 (0.013)
Difference between treatments	-0.03	
95% Confidence Interval	(-0.07, 0.01)	
Change from Baseline HbA1c (%) at Month 12	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.38 (0.140)	-0.20 (0.101)
Difference between treatments	0.18	
95% Confidence Interval	(-0.16, 0.51)	
HbA1c (%) at Month 12	Placebo	Otelixizumab
Mean (SE) at Month 12	6.83 (0.146)	7.02 (0.108)
Difference between treatments	0.18	
95% Confidence Interval	(-0.16, 0.52)	
Change from Baseline HbA1c (%) at Month 6	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.61 (0.132)	-0.45 (0.094)
Difference between treatments	0.16	
95% Confidence Interval	(-0.15, 0.48)	
HbA1c (%) at Month 6	Placebo	Otelixizumab
Mean (SE) at Month 6	6.60 (0.138)	6.77 (0.100)
Difference between treatments	0.17	
95% Confidence Interval	(-0.15, 0.49)	
Change from Baseline HbA1c (%) at Month 3	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.76 (0.117)	-0.69 (0.083)
Difference between treatments	0.07	
95% Confidence Interval	(-0.20, 0.35)	
HbA1c (%) at Month 3	Placebo	Otelixizumab
Mean (SE) at Month 3	6.45 (0.124)	6.54 (0.094)
Difference between treatments	0.09	
95% Confidence Interval	(-0.19, 0.36)	
Change from Baseline IDAA1c at Month 12	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.08 (0.188)	-0.09 (0.132)
Difference between treatments	-0.02	
95% Confidence Interval	(-0.47, 0.43)	
IDAA1c at Month 12	Placebo	Otelixizumab
Mean (SE) at Month 12	8.54 (0.193)	8.55 (0.141)
Difference between treatments	0.01	
95% Confidence Interval	(-0.44, 0.45)	
Change from Baseline IDAA1c at Month 6	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.58 (0.182)	-0.49 (0.127)
Difference between treatments	0.08	
95% Confidence Interval	(-0.35, 0.51)	
IDAA1c at Month 6	Placebo	Otelixizumab
Mean (SE) at Month 6	8.07 (0.186)	8.15 (0.134)
Difference between treatments	0.08	
95% Confidence Interval	(-0.35, 0.51)	
Change from Baseline IDAA1c at Month 3	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.80 (0.136)	-0.94 (0.095)
Difference between treatments	-0.13	

95% Confidence Interval	(-0.45, 0.19)	
IDAA1c at Month 3	Placebo	Otelixizumab
Mean (SE) at Month 3	7.83 (0.144)	7.70 (0.109)
Difference between treatments	-0.12	
95% Confidence Interval	(-0.44, 0.19)	
Change from Baseline ADRR at Month 12	Placebo	Otelixizumab
Mean change from baseline (SE)	3.29 (1.038)	4.22 (0.732)
Difference between treatments	0.93	
95% Confidence Interval	(-1.56, 3.42)	
ADRR at Month 12	Placebo	Otelixizumab
Mean (SE) at Month 12	18.27 (1.075)	19.02 (0.787)
Difference between treatments	0.76	
95% Confidence Interval	(-1.64, 3.15)	
Change from Baseline ADRR at Month 6	Placebo	Otelixizumab
Mean change from baseline (SE)	2.03 (1.133)	2.86 (0.801)
Difference between treatments	0.83	
95% Confidence Interval	(-1.89, 3.56)	
ADRR at Month 6	Placebo	Otelixizumab
Mean (SE) at Month 6	16.58 (1.150)	17.64 (0.840)
Difference between treatments	1.07	
95% Confidence Interval	(-1.50, 3.64)	
Change from Baseline ADRR at Month 3	Placebo	Otelixizumab
Mean change from baseline (SE)	-0.41 (0.826)	0.71 (0.599)
Difference between treatments	1.12	
95% Confidence Interval	(-0.88, 3.11)	
ADRR at Month 3	Placebo	Otelixizumab
Mean (SE) at Month 3	14.29 (0.911)	15.75 (0.714)
Difference between treatments	1.46	
95% Confidence Interval	(-0.45, 3.37)	
Responders (HbA1c/insulin use) at Month 12	Placebo	Otelixizumab
Proportion of subjects n/N (%)	34/80 (42.5)	56/160 (35.0)
Odds ratio	0.81	
95% Confidence Interval	(0.45, 1.46)	
Responders (HbA1c/insulin use) at Month 6	Placebo	Otelixizumab
Proportion of subjects n/N (%)	42/76 (55.3)	74/158 (46.8)
Odds ratio	0.77	
95% Confidence Interval	(0.42, 1.39)	
Responders (HbA1c/insulin use) at Month 3	Placebo	Otelixizumab
Proportion of subjects n/N (%)	45/78 (57.7)	85/161 (52.8)
Odds ratio	0.90	
95% Confidence Interval	(0.47, 1.70)	
Hypoglycaemia	Placebo	Otelixizumab
From baseline to Month 12		
N of events of severe hypoglycaemia m (m/N)	2 (0.0)	5 (0.0)
Incidence of severe hypoglycaemia n (%)	2 (2.2)	4 (2.2)
N of events of documented symptomatic hypoglycaemia m (m/N)	3092 (34.0)	6322 (34.9)
Incidence of documented symptomatic hypoglycaemia	78 (85.7)	163 (90.1)
N of events of asymptomatic hypoglycaemia m (m/N)	4718 (51.8)	9962 (55.0)
Incidence of asymptomatic hypoglycaemia	10 (11.0)	13 (7.2)
From Month 12 to Month 24		
N of events of severe hypoglycaemia m (m/N)	0	0
Incidence of severe hypoglycaemia n (%)	0	0
N of events of documented symptomatic hypoglycaemia m (m/N)	1116 (12.3)	1590 (8.8)
Incidence of documented symptomatic hypoglycaemia	39 (42.9)	83 (45.9)
N of events of asymptomatic hypoglycaemia m (m/N)	2061 (22.6)	4312 (23.8)

Incidence of asymptomatic hypoglycaemia	22 (24.2)	40 (22.1)
Hypoglycaemic excursions (<=70 mg/dL)		
N hypoglycaemic excursions over 7-day periods	Placebo	Otelixizumab
Baseline Mean (SE)	2.7 (0.37)	2.3 (0.22)
Month 3 Mean (SE)	2.3 (0.28)	2.8 (0.27)
Month 6 Mean (SE)	3.0 (0.36)	2.9 (0.27)
Month 12 Mean (SE)	2.9 (0.41)	3.2 (0.32)
Magnitude of greatest hypoglycaemic excursion	Placebo	Otelixizumab
Baseline Mean (SE)	8.1 (0.97)	8.3 (0.73)
Month 3 Mean (SE)	9.4 (0.92)	10.8 (0.90)
Month 6 Mean (SE)	11.9 (1.24)	10.6 (0.77)
Month 12 Mean (SE)	11.2 (1.20)	11.0 (0.92)
Proportion of subjects with hypoglycaemic excursions n/N (%)	Placebo	Otelixizumab
Baseline	56/86 (65.1)	116/170 (68.2)
Month 3	72/90 (80.0)	127/177 (71.8)
Month 6	57/80 (71.3)	121/166 (72.9)
Month 12	56/78 (71.8)	111/161 (68.9)
Hyperglycaemia		
Number of Hyperglycaemic Excursions over 7-Day Periods	Placebo	Otelixizumab
Threshold: >100 mg/dL		
Baseline Mean (SE)	30.4 (1.26)	32.4 (0.96)
Month 3 Mean (SE)	34.0 (1.78)	32.9 (1.15)
Month 6 Mean (SE)	33.5 (1.77)	35.1 (1.41)
Month 12 Mean (SE)	35.6 (1.97)	33.4 (1.27)
Threshold: >130 mg/dL		
Baseline Mean (SE)	16.9 (1.19)	18.3 (0.89)
Month 3 Mean (SE)	20.5 (1.72)	19.9 (1.01)
Month 6 Mean (SE)	20.8 (1.68)	22.7 (1.25)
Month 12 Mean (SE)	24.0 (1.92)	22.2 (1.05)
Threshold: >200 mg/dL		
Baseline Mean (SE)	4.2 (0.68)	4.3 (0.47)
Month 3 Mean (SE)	5.7 (0.85)	5.6 (0.59)
Month 6 Mean (SE)	6.5 (1.07)	7.9 (0.85)
Month 12 Mean (SE)	8.6 (1.42)	6.9 (0.59)
Magnitude of Greatest Hyperglycaemic Excursion	Placebo	Otelixizumab
Threshold: >100 mg/dL		
Baseline Mean (SE)	144.0 (7.84)	138.0 (5.02)
Month 3 Mean (SE)	158.3 (9.26)	158.4 (6.65)
Month 6 Mean (SE)	154.6 (9.34)	175.7 (8.09)
Month 12 Mean (SE)	176.7 (10.02)	177.5 (7.08)
Threshold: >130 mg/dL		
Baseline Mean (SE)	114.0 (7.84)	108.0 (5.02)
Month 3 Mean (SE)	128.3 (9.26)	128.4 (6.65)
Month 6 Mean (SE)	124.8 (9.31)	145.7 (8.09)
Month 12 Mean (SE)	146.8 (10.00)	147.5 (7.07)
Threshold: >200 mg/dL		
Baseline Mean (SE)	51.7 (7.04)	46.2 (4.37)
Month 3 Mean (SE)	65.7 (8.51)	65.7 (6.12)
Month 6 Mean (SE)	63.3 (8.32)	80.1 (7.75)
Month 12 Mean (SE)	81.8 (9.33)	82.6 (6.61)
Proportion of Subjects with Hyperglycaemic Excursions	Placebo	Otelixizumab
Threshold: >100 mg/dL		
Baseline n/N (%)	86/86(100.0)	170/170(100.0)
Month 3 n/N (%)	90/90(100.0)	177/177(100.0)
Month 6 n/N (%)	80/80(100.0)	166/166(100.0)

Month 12 n/N (%)	78/78(100.0)	161/161(100.0)
Threshold: >130 mg/dL		
Baseline n/N (%)	86/86(100.0)	170/170(100.0)
Month 3 n/N (%)	90/90(100.0)	177/177(100.0)
Month 6 n/N (%)	79/80 (98.8)	166/166(100.0)
Month 12 n/N (%)	77/78 (98.7)	160/161 (99.4)
Threshold: >200 mg/dL		
Baseline n/N (%)	59/86 (68.6)	113/170 (66.5)
Month 3 n/N (%)	65/90 (72.2)	130/177 (73.4)
Month 6 n/N (%)	57/80 (71.3)	139/166 (83.7)
Month 12 n/N (%)	60/78 (76.9)	131/161 (81.4)
Change from baseline in interleukin (IL)-6 pg/mL	Placebo	Otelixizumab
Baseline, n	88	177
Mean (SE)	0.73 (0.133)	0.62 (0.102)
Day 1 2hr end-of-infusion (EOI), n	24	50
Mean change from baseline (SE)	0.76 (0.680)	2.78 (0.544)
Day 4 2hr EOI, n	24	44
Mean change from baseline (SE)	-0.13 (0.251)	3.01 (1.107)
Day 8 2HR EOI, n	23	50
Mean change from baseline (SE)	0.45 (0.448)	14.59 (5.266)
Change from baseline in interleukin (IL)-10 pg/mL	Placebo	Otelixizumab
Baseline, n	85	175
Mean (SE)	6.53 (1.222)	4.38 (0.299)
Day 1 2hr EOI, n	23	50
Mean change from baseline (SE)	0.15 (0.342)	4.61 (1.770)
Day 4 2hr EOI, n	23	44
Mean change from baseline (SE)	0.55 (0.629)	1.35 (0.575)
Day 8 2hr EOI, n	22	49
Mean change from baseline (SE)	1.84 (1.019)	25.57 (7.196)
Change from baseline in Tumour Necrosis Factor (TNFα) pg/mL	Placebo	Otelixizumab
Baseline, n	88	177
Mean (SE)	1.805 (0.1452)	2.382 (0.7604)
Day 1 2hr EOI, n	24	50
Mean change from baseline (SE)	-0.126 (0.0719)	2.320 (0.3996)
Day 4 2hr EOI, n	24	44
Mean change from baseline (SE)	0.111 (0.2381)	1.509 (0.5740)
Day 8 2hr EOI, n	23	50
Mean change from baseline (SE)	0.135 (0.2649)	3.614 (0.8920)
PD effects of otelixizumab in T1DM		
Percent of baseline CD4+CD25+FoxP3+ T cells (10^6/L)	Placebo	Otelixizumab
Baseline, n	80	167
Median	31	30
Day 4 2hr EOI, n	28	56
Median % change from baseline	118.8	53.4
Day 8 predose, n	27	57
Median % change from baseline	94.4	49.7
Day 8 2hr EOI, n	70	146
Median % change from baseline	113.2	40.1
Day 14, n	72	153
Median % change from baseline	114.5	101.3
Day 21, n	74	147
Median % change from baseline	114.6	101.9
Day 28, n	75	151
Median % change from baseline	95.1	101.7
Week 6, n	72	148

Median % change from baseline	104.1	106.6
Week 8, n	75	156
Median % change from baseline	110.1	107.1
Week 10, n	75	145
Median % change from baseline	109.9	102.7
Week 12, n	75	150
Median % change from baseline	102.5	85.5
Month 6, n	72	146
Median % change from baseline	137.9	133.3
Month 12, n	70	149
Median % change from baseline	122.0	106.9
Percent of baseline CD4+CD25^{hi}+FoxP3+ T cells (10^6/L)	Placebo	Otelixizumab
Baseline, n	80	167
Median	14	13
Day 4 2hr EOI, n	28	56
Median % change from baseline	151.9	60.8
Day 8 predose, n	27	57
Median % change from baseline	93.8	43.5
Day 8 2hr EOI, n	69	146
Median % change from baseline	110.7	35.9
Day 14, n	71	153
Median % change from baseline	118.4	109.7
Day 21, n	74	147
Median % change from baseline	110.0	98.8
Day 28, n	74	151
Median % change from baseline	101.1	108.7
Week 6, n	72	148
Median % change from baseline	106.9	110.7
Week 8, n	74	156
Median % change from baseline	131.7	120.3
Week 10, n	74	145
Median % change from baseline	97.7	107.0
Week 12, n	74	150
Median % change from baseline	113.6	90.9
Month 6, n	71	146
Median % change from baseline	150.9	153.2
Month 12, n	69	149
Median % change from baseline	166.4	160.6
Percent of baseline cell-bound otelixizumab on CD4+ T cells (Mean Equivalence of Soluble Fluorescence [MESF])	Placebo	Otelixizumab
Baseline, n	30	68
Mean (SE)	11285 (1975.0)	8488 (689.6)
Day 1 2hr EOI, n	20	57
Mean % change from baseline (SE)	125.1 (18.00)	914.8 (269.18)
Day 4 2hr EOI, n	23	54
Mean % change from baseline (SE)	174.3 (41.95)	2719.8 (369.41)
Day 8 predose, n	26	54
Mean % change from baseline (SE)	151.5 (39.49)	471.5 (98.53)
Day 8 2hr EOI, n	26	57
Mean % change from baseline (SE)	167.9 (47.67)	1387.5 (274.21)
CD3/TCR saturation on CD4+ T cells: percent of baseline (MESF)	Placebo	Otelixizumab
Baseline, n	30	68
Mean (SE)	210267 (19045.6)	197233 (9316.0)
Day 1 2hr EOI, n	20	57

Mean % change from baseline (SE)	93.4 (2.40)	90.9 (3.82)
Day 4 2hr EOI, n	23	54
Mean % change from baseline (SE)	109.7 (11.91)	50.2 (4.90)
Day 8 predose, n	26	54
Mean % change from baseline (SE)	97.7 (10.66)	59.0 (5.31)
Day 8 2hr EOI, n	26	56
Mean % change from baseline (SE)	98.0 (13.03)	21.7 (3.33)
CD3/TCR saturation on CD8+ T cells: percent of baseline (MESF)	Placebo	Otelixizumab
Baseline, n	30	68
Mean (SE)	165834 (16157.7)	147048 (6853.3)
Day 1 2hr EOI, n	20	57
Mean % change from baseline (SE)	92.4 (2.38)	91.4 (3.82)
Day 4 2hr EOI, n	23	54
Mean % change from baseline (SE)	116.7 (14.53)	51.6 (5.23)
Day 8 predose, n	26	54
Mean % change from baseline (SE)	97.4 (11.84)	60.8 (6.11)
Day 8 2hr EOI, n	26	56
Mean % change from baseline (SE)	98.2 (14.63)	23.0 (3.72)
CD3/TCR modulation on CD4+ T cells: percent of baseline (MESF)	Placebo	Otelixizumab
Baseline, n	30	68
Mean (SE)	42768 (2638.3)	44510 (1375.8)
Day 1 2hr EOI, n	20	57
Mean % change from baseline (SE)	94.2 (2.95)	91.1 (2.90)
Day 4 2hr EOI, n	23	54
Mean % change from baseline (SE)	103.8 (8.93)	70.8 (3.89)
Day 8 predose, n	26	54
Mean % change from baseline (SE)	101.4 (6.09)	61.0 (2.65)
Day 8 2hr EOI, n	26	57
Mean % change from baseline (SE)	103.4 (5.87)	32.2 (2.52)
CD3/TCR smodulation on CD8+ T cells: percent of baseline (MESF)	Placebo	Otelixizumab
Baseline, n	30	68
Mean (SE)	31861 (1866.5)	31913 (971.5)
Day 1 2hr EOI, n	20	57
Mean % change from baseline (SE)	95.2 (2.72)	93.7 (3.06)
Day 4 2hr EOI, n	23	54
Mean % change from baseline (SE)	111.1 (10.56)	77.1 (4.33)
Day 8 predose, n	26	54
Mean % change from baseline (SE)	101.8 (6.19)	62.3 (2.68)
Day 8 2hr EOI, n	26	57
Mean % change from baseline (SE)	103.0 (6.05)	36.2 (2.52)
Safety Results: Adverse events (AEs) were collected from the beginning of the first infusion until completion of the Month 24 visit.		
	Placebo	Otelixizumab
Most Frequent Adverse Events	n (%)	n (%)

Subjects with any AE(s), n (%)	84 (92.3)	178 (98.3)
Headache	45 (49.5)	155 (85.6)
Nausea	20 (22.0)	60 (33.1)
Nasopharyngitis	33 (36.3)	50 (27.6)
Fatigue	20 (22.0)	42 (23.2)
Vomiting	14 (15.4)	35 (19.3)
Pyrexia	11 (12.1)	35 (19.3)
Upper respiratory tract infection	13 (14.3)	30 (16.6)
Oropharyngeal pain	24 (26.4)	27 (14.9)
Chills	7 (7.7)	24 (13.3)
Hypoglycaemia	8 (8.8)	23 (12.7)
Myalgia	15 (16.5)	21 (11.6)
Arthralgia	3 (3.3)	21 (11.6)
Dizziness	12 (13.2)	20 (11.0)
Cough	12 (13.2)	19 (10.5)
Lymphadenopathy	13 (14.3)	18 (9.9)
Serious Adverse Events (SAEs) n (%) [n considered by the investigator to be related to study medication]		
	Placebo	Otelixizumab
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0 [0]	0 [0]
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	8 (8.8) [0]	18 (9.9) [5]
Anal abscess	0 [0]	1 (0.6) [0]
Appendicitis	1 (1.1) [0]	2 (1.1) [0]
Gastroenteritis viral	1 (1.1) [0]	0 [0]
Septic embolus	0 [0]	1 (0.6) [1]
Tonsillitis	1 (1.1) [0]	0 [0]
Viral upper respiratory tract infection	1 (1.1) [0]	0 [0]
Gastritis erosive	0	1 (0.6) [0]
Peritonitis	0	1 (0.6) [0]
Cytokine release syndrome	0 [0]	3 (1.7) [3]
Alcohol poisoning	0 [0]	1 (0.6) [0])
Ligament rupture	0 [0]	1 (0.6) [0]
Road traffic accident	0 [0]	1 (0.6) [0]
Hyperglycaemia	1 (1.1) [0]	0
Anal fistula	0 [0]	1 (0.6) [0]
Gastritis erosive	0 [0]	1 (0.6) [0]
Hypoglycaemia	0 [0]	1 (0.6) [0]
Hypoglycaemic seizure	0 [0]	1 (0.6) [0]
Ketoacidosis	0	1 (0.6) [0]
Neurological symptom	1 (1.1) [0])	0 [0]
Paraesthesia	0 [0]	1 (0.6) [0]
Tremor	0	1 (0.6) [1]
Alcohol abuse	0 [0]	1 (0.6) [0]
Depression	0	1 (0.6) [0]
Major depression	1 (1.1) [0]	0 [0]
Suicidal ideation	0	1 (0.6) [0]
Cholecystitis	2 (2.2) [0]	0
Intervertebral disc protrusion	0 [0]	1 (0.6) [0]
Muscular weakness	0	1 (0.6) [1]
Abortion missed	0 [0]	1 (0.6) [0]

Conclusion:
There were no statistically significant differences between the treatment groups for the primary or any of the secondary

efficacy endpoints. There were no deaths and the incidence of SAEs was similar between the treatment groups. The higher incidence of AEs in the otelixizumab group compared with the placebo group was due to a higher incidence of AEs associated with cytokine release syndrome.