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.: OTX115494
Title: DEFEND-2: Durable-Response Therapy Evaluation For Early- or New-Onset Type 1 Diabetes (12 month report)
Rationale: Otelixizumab is an anti-human CD3 monoclonal antibody 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 as a confirmatory study to Study OTX115495 (DEFEND-1). Both studies measured the effect of otelixizumab on preservation of β cell function in subjects with T1DM.
Phase: III
Study Period: 17 May 2010 - 09 Mar 2012 (The study was terminated after the last subject had completed evaluations at Month 12.)
Study Design: This was a randomized, placebo-controlled, double-blind, multicenter study of the efficacy and safety of otelixizumab in adolescents and adults with new-onset T1DM. After a screening period of up to 35 days, eligible subjects were randomized in a 2:1 ratio to receive either otelixizumab or placebo as one infusion per day over 8 consecutive days. After the 8-day dosing period, subjects were to be followed short-term at weekly or monthly visits through Month 12 for the primary evaluation of efficacy and safety and then long-term at Months 15, 18, and 24 for further evaluation of efficacy and safety. Following review of the DEFEND-1 results, enrollment of new subjects was suspended in April 2011 pending the outcome of the Independent Data Monitoring Committee (IDMC) analysis of the Month 6 data from all subjects participating in DEFEND-2; however, evaluations continued for subjects enrolled in the trial before the enrollment suspension. The IDMC analysis did not show any statistically significant differences between treatment groups for the primary endpoint and no new safety signals were detected, thus DEFEND-2 was terminated by the sponsor after all subjects completed evaluations at Month 12. Data through Month 18 are presented here.
Centres: Subjects were enrolled at 73 centers in 10 countries. The countries (number of centers) were as follows: Belgium (4), Canada (4), Germany (1), Denmark (2), Spain (7), Finland (2), United Kingdom (5), Italy (2), Sweden (7), and United States of America (39).
Indication: Type 1 diabetes mellitus
Treatment: Otelixizumab and matching placebo were supplied as a sterile, preservative-free aqueous solution for intravenous administration that was diluted in 0.9% saline solution for intravenous (IV) infusion over 30 minutes on Days 1-8 of the study. Subjects were to remain at the study center for observation for at least 2 to 4 hours after completing each infusion. 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.
Objectives: The primary objective was to demonstrate that subjects who received an 8-day series of otelixizumab infusions had greater improvement than subjects who received 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): C-peptide AUC at Month 3 and Month 6 was a sub-analysis of the primary objective. Key secondary endpoints were responder status (where a responder was defined as a subject with glycosylated hemoglobin (HbA1c) ≤6.5% and a mean daily insulin use over 7 consecutive days of <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 hypoglycemia in the categories “severe hypoglycemia” and “documented symptomatic hypoglycemia”; composite outcome of baseline-adjusted HbA1c and exogenous insulin use; composite outcome of baseline-adjusted C-peptide AUC, HbA1c, and exogenous insulin use; HbA1c and mean daily insulin use over time; C-peptide AUC and mean daily insulin use over time; and HbA1c and C-peptide AUC over time. The pharmacodynamic activity (PD) of otelixizumab was assessed by absolute counts and percentages of lymphocyte subsets and CD3/TCR modulation (European sites only).
Statistical Methods: A sample size of 363 subjects (249 adolescents and 114 adults) was prospectively defined for this study to provide 98% power to detect a treatment effect for the primary endpoint of 0.22 (nmol/L*min)/min and at least 90% power to detect an effect of 0.176 (nmol/L*min)/min at a 2-sided significance level of 0.05 and assuming a 25% dropout rate. A treatment effect of 0.22 (nmol/L*min)/min would represent an improvement in preservation of

normalized stimulated C-peptide AUC of approximately 37% relative to placebo. However, this sample size was not achieved because recruitment of new subjects was suspended after 179 subjects had been enrolled in the study. Efficacy and PD analyses were conducted on the intent-to-treat (ITT) population which consisted of all subjects who were randomized and received any part of at least 1 infusion of study drug. Safety analyses were performed on the safety population which consisted of all subjects for whom there was evidence that they 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 considered significant if the two-sided p-value was ≤ 0.05. Responders were compared by 2-sided tests of equality based on the normal approximation to the binomial distribution. Exogenous insulin use and HbA1c endpoints were compared using a repeated-measures mixed-effects model similar to that of the primary endpoint. The composite outcomes HbA1c/exogenous insulin use, and C-peptide AUC/HbA1c/exogenous insulin use were compared between treatment groups using the O'Brien nonparametric ranks test procedure.

Study Population: Eligible subjects included adolescents and adults aged 12-45 years who weighed at least 31 kg and who had a diagnosis of new-onset T1DM (within 90 days prior to first dose of study drug) that required insulin therapy. Adolescents (12-17 years) were to be Tanner Stage ≥ 2. All subjects required evidence of residual β cell function (stimulated C-peptide >0.20 nmol/L during a mixed meal tolerance test initiated when blood glucose was >70 mg/dL but $\leq$200 mg/dL, with maximum stimulated C-peptide $\leq$3.5 nmol/L) and a positive test for one or more of the autoantibodies typically associated with T1DM.

Number of Subjects:	**Placebo**	**Otelixizumab**
Planned, N	121	222
Randomised, N	61	118
Completed, n (%)	50 (82.0)	103 (87.3)
Total Number Subjects Withdrawn, N (%)	11 (18.0)	15 (12.7)
Withdrawn due to Adverse Events n (%)	1 (1.6)	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	10 (16.4)	15 (12.7)
Demographics	**Placebo**	**Otelixizumab**
N (ITT)	61	118
Females: Males	24:37	50:68
Mean Age, years (SD)	22.5 (8.22)	23.6 (8.34)
White, n (%)	54 (88.5)	111 (94.1)
Adolescents, n (%)	18 (29.5)	36 (30.5)
Adolescent mean age, years (SD)	14.6 (1.62)	14.4 (1.97)
Primary Efficacy Results:		
Change from baseline C-peptide AUC ([nmol/L*min]/min) at Month 12	**Placebo**	**Otelixizumab**
n at Month 12	45	96
LS Mean change from baseline (SE)	-0.14 (0.036)	-0.23 (0.026)
Difference between treatments	-0.09	
95% Confidence Interval	(-0.17, 0.00)	
p-value	0.051	
Secondary Outcome Variable(s):		
Change from baseline C-peptide AUC ([nmol/L*min]/min) at Month 6	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	-0.04 (0.037)	-0.10 (0.027)
Difference between treatments	-0.06	
95% Confidence Interval	(-0.15, 0.03)	
Change from baseline C-peptide AUC ([nmol/L*min]/min) at Month 3	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	0.05 (0.031)	-0.05 (0.023)
Difference between treatments	-0.10	
95% Confidence Interval	(-0.18, -0.02)	

Change from baseline mean daily insulin use (IU/kg) at Month 12	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	0.01 (0.036)	0.05 (0.028)
Difference between treatments	0.04	
95% Confidence Interval	(-0.05, 0.13)	
Change from baseline mean daily insulin use (IU/kg) at Month 6	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	0.01 (0.027)	-0.04 (0.021)
Difference between treatments	-0.04	
95% Confidence Interval	(-0.11, 0.02)	
Change from baseline mean daily insulin use (IU/kg) at Month 3	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	-0.04 (0.020)	-0.08 (0.016)
Difference between treatments	-0.03	
95% Confidence Interval	(-0.08, 0.02)	
Change from baseline HbA1c % at Month 12	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	-0.61 (0.188)	-0.47 (0.133)
Difference between treatments	0.13	
95% Confidence Interval	(-0.33, 0.59)	
Change from baseline HbA1c % at Month 6	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	-0.65 (0.185)	-0.65 (0.134)
Difference between treatments	-0.00	
95% Confidence Interval	(-0.46, 0.45)	
Change from baseline HbA1c % at Month 3	**Placebo**	**Otelixizumab**
LS Mean change from baseline (SE)	-0.82 (0.140)	-1.01 (0.101)
Difference between treatments	-0.18	
95% Confidence Interval	(-0.52, 0.16)	
Proportion of responders (HbA1c/insulin use) at Month 12	**Placebo**	**Otelixizumab**
% (n/N)	37% (10/27)	43% (23/54)
Odds ratio	1.56	
95% Confidence Interval	(0.54, 4.52)	
Proportion of responders (HbA1c/insulin use) at Month 6	**Placebo**	**Otelixizumab**
% (n/N)	31% (11/35)	43% (26/61)
Odds ratio	0.95	
95% Confidence Interval	(0.37, 2.42)	
Proportion of responders (HbA1c/insulin use) at Month 3	**Placebo**	**Otelixizumab**
% (n/N)	46% (19/41)	62% (42/68)
Odds ratio	1.29	
95% Confidence Interval	(0.50, 3.37)	
Hypoglycemia from baseline to Month 12	**Placebo**	**Otelixizumab**
Severe hypoglycemia events, number of events (number of events/total number of subjects in treatment group)	33 (0.5)	11 (0.1)
Subjects with severe hypoglycemia events, n (%)	7 (11.5)	7 (5.9)
Subjects with documented symptomatic hypoglycemia events by IVRS, n (%)	22 (36.1)	34 (28.8)
Subjects with documented symptomatic hypoglycemia events by eCRF, n (%)	28 (45.9)	51 (43.2)
Composite endpoint of HbA1c and exogenous insulin use at Month 12	**Placebo**	**Otelixizumab**
n	23	45
Mean (SD)	96 (51.2)	110 (55.3)
Composite endpoint of HbA1c and exogenous insulin use at Month 6	**Placebo**	**Otelixizumab**
n	28	48
Mean (SD)	119 (48.4)	110 (49.8)

Composite endpoint of C-peptide AUC, HbA1c, and exogenous insulin use at Month 12	**Placebo**	**Otelixizumab**
n	23	42
Mean (SD)	180 (42.5)	170 (46.0)
Composite endpoint of C-peptide AUC, HbA1c, and exogenous insulin use at Month 6	**Placebo**	**Otelixizumab**
n	26	48
Mean (SD)	206 (48.6)	186 (41.6)
Percent of baseline CD4+ T cells	**Placebo**	**Otelixizumab**
Day 1, 2 hours (hrs) after end of infusion (EOI), n	26	56
Mean % of baseline (SD)	97.4963 (6.43124)	109.8031 (16.05506)
Day 4, 2 hrs after EOI, n	24	51
Mean % of baseline (SD)	98.6930 (9.53747)	94.0815 (13.45334)
Day 8, predose, n	24	50
Mean % of baseline (SD)	96.0634 (9.21260)	93.5757 (12.82548)
Day 8, 2 hrs after EOI, n	24	49
Mean % of baseline (SD)	94.1315 (11.87643)	78.1095 (16.12853)
Day 14, n	23	49
Mean % of baseline (SD)	97.9561 (8.81605)	101.5698 (11.20377)
Day 21, n	20	46
Mean % of baseline (SD)	96.3598 (10.14995)	103.7766 (14.48674)
Day 28, n	21	42
Mean % of baseline (SD)	97.6741 (10.06876)	101.4786 (13.72362)
Week 6, n	14	40
Mean % of baseline (SD)	96.5517 (10.33585)	100.0359 (15.26020)
Week 8, n	14	39
Mean % of baseline (SD)	94.7479 (10.30723)	101.4984 (11.90626)
Week 10, n	15	38
Mean % of baseline (SD)	96.9659 (8.50965)	100.2270 (14.59375)
Week 12, n	10	27
Mean % of baseline (SD)	98.7919 (7.56390)	98.3279 (11.51927)
Month 6, n	8	12
Mean % of baseline (SD)	92.9068 (8.79990)	99.9111 (12.04794)
Month 12, n	2	3
Mean % of baseline (SD)	90.5724 (1.13745)	103.7704 (25.42227)
Month 18, n	1	1
Mean % of baseline (SD)	100.1221 (NA)	102.4046 (NA)
Percent of baseline CD8+ T cells	**Placebo**	**Otelixizumab**
Day 1, 2 hours (hrs) after end of infusion (EOI), n	26	56
Mean % of baseline (SD)	101.1838 (9.77317)	79.8789 (14.69458)
Day 4, 2 hrs after EOI, n	24	51
Mean % of baseline (SD)	104.6472 (18.64389)	65.9198 (14.62383)
Day 8, predose, n	24	50
Mean % of baseline (SD)	101.6777 (13.83653)	93.1511 (32.71545)
Day 8, 2 hrs after EOI, n	24	49
Mean % of baseline (SD)	100.9542 (16.09261)	92.8878 (27.05005)
Day 14, n	23	49
Mean % of baseline (SD)	97.2494 (15.24198)	101.4551 (24.83261)
Day 21, n	20	46
Mean % of baseline (SD)	101.0556 (14.45479)	107.5427 (30.03484)
Day 28, n	21	42
Mean % of baseline (SD)	101.4197 (16.74238)	107.7523 (34.21077)
Week 6, n	14	40
Mean % of baseline (SD)	98.5909 (17.36351)	107.7939 (21.02547)

Week 8, n	14	39
Mean % of baseline (SD)	97.4494 (12.80327)	100.7948 (14.05912)
Week 10, n	15	38
Mean % of baseline (SD)	104.9878 (16.69468)	106.6599 (22.31731)
Week 12, n	10	27
Mean % of baseline (SD)	100.3198 (11.24180)	102.5394 (15.01021)
Month 6, n	8	12
Mean % of baseline (SD)	104.7974 (12.69854)	120.8622 (59.75089)
Month 12, n	2	3
Mean % of baseline (SD)	111.6215 (3.83961)	168.3136 (84.70470)
Month 18, n	1	1
Mean % of baseline (SD)	122.1959 (NA)	90.8087 (NA)
CD3/TCR modulation on CD4+ T cells (measured as molecules of equivalent soluble fluorochrome)	**Placebo**	**Otelixizumab**
Day 1 predose, n	28	56
Median	8121	8166
Day 1, 2 hrs after EOI, n	26	56
Median	7215.5	8384
Day 4, 2 hrs after EOI, n	24	51
Median	9778	5342
Day 8, predose, n	25	50
Median	7689	5046.5
Day 8, 2 hrs after EOI, n	25	48
Median	8248	1597.5
Day 14, n	25	50
Median	9327	7421
Day 21, n	21	47
Median	8487	7974
Day 28, n	22	43
Median	7816	7072
Week 6, n	0	1
Median	-	8616
Week 8, n	0	1
Median	-	10721
CD3/TCR modulation on CD8+ T cells (measured as molecules of equivalent soluble fluorochrome)	**Placebo**	**Otelixizumab**
Day 1 predose, n	28	56
Median	3763.5	3837.5
Day 1, 2 hrs after EOI, n	26	56
Median	3939	4143.5
Day 4, 2 hrs after EOI, n	24	51
Median	4506	2201
Day 8, predose, n	25	50
Median	3455	2411.5
Day 8, 2 hrs after EOI, n	25	48
Median	3598	932.5
Day 14, n	25	50
Median	3905	3400.5
Day 21, n	21	47
Median	3891	3841
Day 28, n	22	43
Median	3703.5	3723
Week 6, n	0	1
Median	-	4451

Week 8, n	0	1
Median	-	5439
An on therapy adverse event (AE) was defined as an AE with onset between the beginning of the first infusion of study drug and the completion of the subject's final visit. The same definition of on therapy was applied to serious adverse events (SAEs).		
	Placebo	**Otelixizumab**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n (%)	54 (89)	112 (95)
Headache	34 (56)	93 (79)
Nausea	16 (26)	38 (32)
Nasopharyngitis	15 (25)	37 (31)
Fatigue	11 (18)	28 (24)
Pyrexia	2 (3)	21 (18)
Vomiting	2 (3)	19 (16)
Chills	3 (5)	16 (14)
Oropharyngeal pain	7 (11)	16 (14)
Hypoglycaemia	6 (10)	13 (11)
Back pain	1 (2)	12 (10)
Dizziness	4 (7)	12 (10)
Abdominal pain	5 (8)	11 (9)
Upper respiratory tract infection	16 (26)	9 (8)
Lymphadenopathy	9 (15)	9 (8)
Sinusitis	7 (11)	3 (3)
Serious Adverse Events – On-Therapy **n (%) [n considered by the investigator to be related to study medication]** Subjects were counted once for each event and once overall/related		
	Placebo	**Otelixizumab**
	n (%) [related]	**n (%) [related]**
Subjects with non-fatal SAEs, n (%)	4 (7) [0]	11 (9) [3]
Cytokine release syndrome	0 [0]	2 (2) [2]
Convulsion	0 [0]	1 (1) [0]
Diabetic ketoacidosis	0 [0]	1 (1) [0]
Dyspnoea	0 [0]	1 (1) [0]
Headache	0 [0]	1 (1) [1]
Hyperglycaemia	1 (2) [0]	1 (1) [0]
Hypoglycaemia	0 [0]	1 (1) [0]
Loss of consciousness	0 [0]	1 (1) [0]
Malaise	0 [0]	1 (1) [0]
Malignant melanoma in situ	0 [0]	1 (1) [1]
Pregnancy induced hypertension	0 [0]	1 (1) [0]
Scoliosis	0 [0]	1 (1) [0]
Thyroid cancer	0 [0]	1 (1) [0]
Urticaria	0 [0]	1 (1) [0]
Vomiting	0 [0]	1 (1) [0]
Atrial septal defect	1 (2) [0]	0 [0]
Major depression	1 (2) [0]	0 [0]
Overdose	1 (2) [0]	0 [0]
Suicidal ideation	1 (2) [0]	0 [0]
	n (%) [related]	**n (%) [related]**
Subjects with fatal SAEs, n (%)	0 [0]	0 [0]

Conclusion:
There were no statistically significant differences favoring otelixizumab over placebo for the primary or any of the secondary efficacy endpoints. No deaths were reported during the study 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.