Study No.: OTX115496

Title: DEFEND-1 Long Term Follow Up: Durable-Response Therapy Evaluation for Early or New Onset Type 1 Diabetes Extension Study

Rationale: The study was an extension to Study DEFEND-1 to investigate the long-term safety and efficacy of otelixizumab in subjects who participated in Study DEFEND-1.

Phase: III

Study Period: 30-Oct-2010 to 30-Sep-2011

Study Design: The study, an extension to Study DEFEND-1, was to evaluate the efficacy and safety of otelixizumab in adolescents and adults with new onset type 1 diabetes mellitus (NOT1DM). In Study DEFEND-1, subjects received 8 consecutive day treatment for a cumulative dose of otelixizumab 3.1 mg or placebo and were followed for 24 months. In the current study, subjects were to be followed up for additional 24 months. There were to be 3 clinical visits: Study Entry (at least 24 months after the administration of study drug in Study DEFEND-1), Month 36, and Month 48. Subjects were to be contacted by phone at 3-month intervals between the clinical visits to assess adverse events (AEs), concomitant medication use, and other medically relevant occurrences. However, the study was prematurely terminated as Study DEFEND-1 failed to meet its primary efficacy endpoint of change in C-peptide at Month 12 in patients with NOT1DM.

Centres: 18 centers in 4 countries: 1 in Finland, 3 each in Canada and Sweden, and 11 in the US.

Indication: type 1 diabetes mellitus

Treatment: No investigational product was administered in this long term follow up study.

Objectives: The primary objective of this study was to demonstrate that subjects who received an 8-day series of otelixizumab infusions in DEFEND-1 had greater preservation of endogenous insulin secretion than subjects who received placebo, as assessed by area under the concentration-time curve (AUC) for mixed meal-stimulated C-peptide, at 48 months after study drug administration.

Primary Outcome/Efficacy Variable: The primary efficacy endpoint was change from Study DEFEND-1 baseline in 2-hour mixed meal-stimulated C-peptide AUC at Month 48. This AUC was normalized for time interval by dividing it by 120 minutes (the number of minutes over which it is determined), and was adjusted by inclusion of baseline C-peptide AUC as a covariate in the analysis.

Secondary Outcome/Efficacy Variable(s):

- Stimulated C-peptide AUC at Month 36. This AUC was normalized and adjusted.
- Responder status at Month 36 and Month 48. At the given time point, a subject was considered a responder if:
  - $HbA_{1c} \leq 6.5\%$ and
  - Mean daily insulin use < 0.5 IU/kg/day over 7 consecutive days during the 2 weeks preceding the visit.
- Mean daily insulin used over 7 consecutive days during the 2 weeks preceding the visit at Month 36 and Month 48. The mean daily insulin in units of IU/kg/day was calculated as the mean of the values of amount of insulin used per day on each of the 7 consecutive days.
- HbA_{1c} level at Month 36 and Month 48.

Statistical Methods: As the pivotal study, DEFEND-1, of otelixizumab in type 1 diabetes did not meet its primary endpoint, the current follow up study was consequently terminated. Therefore, study population and safety data for all enrolled subjects were summarized and listed. No efficacy analyses were performed as no subject had any efficacy assessments at the time of study termination.

Study Population:

	Previous Placebo	Previous Otelixizumab	All Enrolled Subjects
Number of Subjects Enrolled:	11	18	29
Total Number Subjects Withdrawn, N (%)	11 (38%)	18 (62%)	29 (100%)
Withdrawn due to Adverse Events n (%)	0	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for the study administrative reason n (%)	11 (38%)	18 (62%)	29 (100%)

Demographics

	Previous Placebo	Previous Otelixizumab	All Enrolled Subjects
N (ITT)	11	18	29
Females: Males	3:8	6:12	9:20
Mean Age, years (SD)	26.0 (5.74)	27.9 (4.24)	27.2 (4.86)

Race, n (%) White Multi-Racial	 11 (100) 0	 17 (94) 1 (6)	 28 (97) 1 (3)
Primary Efficacy Results: No efficacy analyses were performed.			
Safety Results:			
Most Frequent Adverse Events (Occurring in >=5% Incidence in any Previous Treatment Group), n (%)			
	Previous Placebo	Previous Otelixizumab	All Enrolled Subjects
Subjects with any AE(s), n (%)	5 (45.5)	9 (50.0)	14 (48.3)
Insomnia	1 (9.1)	1 (5.6)	2 (6.9)
Seasonal allergy	1 (9.1)	1 (5.6)	2 (6.9)
Abdominal pain	0	1 (5.6)	1 (3.4)
Anxiety	0	1 (5.6)	1 (3.4)
Cardiac murmur	0	1 (5.6)	1 (3.4)
Depression	0	1 (5.6)	1 (3.4)
Fungal skin infection	0	1 (5.6)	1 (3.4)
Hypercholesterolaemia	0	1 (5.6)	1 (3.4)
Hypoglycaemia	0	1 (5.6)	1 (3.4)
Lipohypertrophy	0	1 (5.6)	1 (3.4)
Muscle twitching	0	1 (5.6)	1 (3.4)
Nasopharyngitis	0	1 (5.6)	1 (3.4)
Ovarian cyst	0	1 (5.6)	1 (3.4)
Pain in extremity	0	1 (5.6)	1 (3.4)
Sciatica	0	1 (5.6)	1 (3.4)
Skin hyperpigmentation	0	1 (5.6)	1 (3.4)
Serious Adverse Events, n (%) [n considered by the investigator to be related to study medication]			
	Previous Placebo	Previous Otelixizumab	All Enrolled Subjects
Subjects with non-fatal SAEs, n (%)	0	1 (5.6)	1 (3.4%)
Abdominal pain	0	1 (5.6) [0]	1 (3.4%) [0]
Subjects with fatal SAEs, n (%)	0	0	0

Conclusion: No new or unexpected safety signals were identified in the current study.