I. Protocol Synopsis

Title	***Effects of Rituximab on the Progression of Type 1 Diabetes in New Onset Subjects***
Version Date	30 August 2009
IND Sponsor	TrialNet
Conducted By	TrialNet
Status	Accrual Closed; Subjects in Long Term Follow-up
Final Accrual	87 randomized: 54 Male, 33 Female. • 57 active: 32 responder, 20 non-responder, 5 response not determined, • 30 placebo: 12 responder, 18 non-responder.
Study Design	The study is a two-arm, multicenter, randomized, double-masked, placebo-controlled clinical trial. Both groups will receive standard intensive diabetes treatment with insulin and dietary management.
Treatment Description	Rituximab (RITUXAN®, Genentech and Biogen Idec) is a chimeric murine/human monoclonal antibody approved for the treatment of B cell non-Hodgkin's lymphoma. The antibody binds to the CD20 antigen on the surface of B cells and mediates B cell depletion. Participants randomly assigned to rituximab treatment will receive four doses of 375mg/m^2 IV each a week apart.
Study Duration	Total duration is approximately 4 years (2 years accrual and 2 years follow-up). Follow-up for up to 4 years will continue for those who have persistence of beta cell function at 2 years and/or detectable immunologic effects of treatment by descriptive analysis until the disappearance of detectable beta cell function or resolution of immunologic changes.
Objective	To assess the safety, efficacy, and mode of action of rituximab, anti-CD20 monoclonal antibody, for the treatment of individuals with new onset type 1 diabetes.
Primary Outcome	The primary statistical hypothesis to be assessed in this study is whether the mean C-peptide value for study subjects on rituximab differs significantly from the mean value for placebo subjects assessed at one year of follow-up.
Secondary Goals	The study will examine the effect of the proposed treatment on surrogate markers for immunologic effects, namely disease-specific outcomes and immunological outcomes.
Major Inclusion Criteria	(1) Type 1 diabetes within past 3 months (2) Age 8-45 years (3) At least one diabetes associated autoantibody

TN-05 Anti-CD20 – Protocol Synopsis & Specimen Collection Schedule

II. Specimen Collection Schedule

~Month of Trial:	*Specimen Disposition* [2]																															
Week of Trial:	***Tested***	***Stored***	**-1**	**0**	**1**	**2**	**3**	**5**	**6**	**7**	**8**	**10**	**12**	**13**	**14**	**16**	**19**	**26**	**39**	**52**	**53**	**54**	**56**	**58**	**59**	**60**	**62**	**65**	**78**	**91**	**104**	**Long Term Follow-up**[7]
Whole Blood: CBC with Differential	x		2	2	2	2	2	2				2	2					2	2	2									2		2	
Serum: Chemistries	x		4										X					X		X											X	
Seum: HIV, Hep B and C Serology	x		4																													
Serum: Autoantibodies	x	x	2.6					2.6					2.6					2.6	2.6	2.6									2.6		2.6	2.6
Whole Blood: HbA1c	x		1.2										1.2					1.2	1.2	1.2									1.2		1.2	1.2
Plasma: 4-hr Mixed Meal Tolerance Test	x		26.4																	26.4											26.4	
Plasma: 2-hr Mixed Meal Tolerance Test	x												16.8					16.8											16.8			16.8
Whole Blood: HLA Determination & FcR Genotype Testing	x	x	6																													
Whole Blood: EBV/CMV PCR	x	x		2		2		2					2				2	2	2				2						2		2	
Serum: EBV/CMV Viral Serology	x	x		4		4		4					4				4	4	4				4						4		4	
Serum: Other Serology[1]	x	x		4														4					4						4		4	
Serum: Rituximab PK Analysis & Anti-rituximab (HACA) Levels	x			4														4	4													
Tetanus Immunization Course[2]	x																			3*			3									
Hepatitis A Immunization Course[3]	x																			3*			3						3*		3*	
PhiX174 Immunization Course[4]	x								3*	3	3	3	3*	3	3	3				3*	3	3	3	X*	3	3	3					
Whole Blood: PBMC/Plasma[5]		x		X				X					X					X		X									X		X	
Whole Blood: RNA		x		6				6					6					6		6									6		6	

Collection volumes represent total volume of whole blood (mL) collected for adult subjects. For children, no more than 3 mL/kg will be drawn at any single visit and no more than 7 mL/kg over a 6 week period.

[1] Antibody titers to other childhood immunizations and illnesses will be measured on these samples.

[2] Tetanus immunization is a single intramuscular immunization designated by * with titers obtained prior to and 4 weeks after immunization.

[3] Hepatitis A immunization course consists of two intramuscular immunizations designated by * administered >6 months apart. The 2nd immunization can be done at either month 18 or 24 visit. Titers may be obtained before and after the immunizations.

[4] PhiX immunization course consists of two intravenous immunizations designated by * separated by 6 weeks. Blood samples are drawn prior to and at 1, 2, and 4 weeks after each immunization.

[5] PBMC and plasma are extracted locally by each collecting site.

[6] Follow-Up After 24 Months: Visits may be conducted approximately every 6 months.

[7] Long term follow up: Whenever feasible, subjects will be contacted annual to ascertain health and diabetes status. Samples for mechanistic studies and to ascertain diabetes control may also be obtained with blood volumes not to exceed 3 mL/kg body weight for children. The samples may include serum, PBMC, and RNA. Subjects who have persistence of beta cell function will undergo MMTT no more than every six months.