Supplementary Online Content

Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group. Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.17070

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Per Protocol Analysis

Adherence - Methods

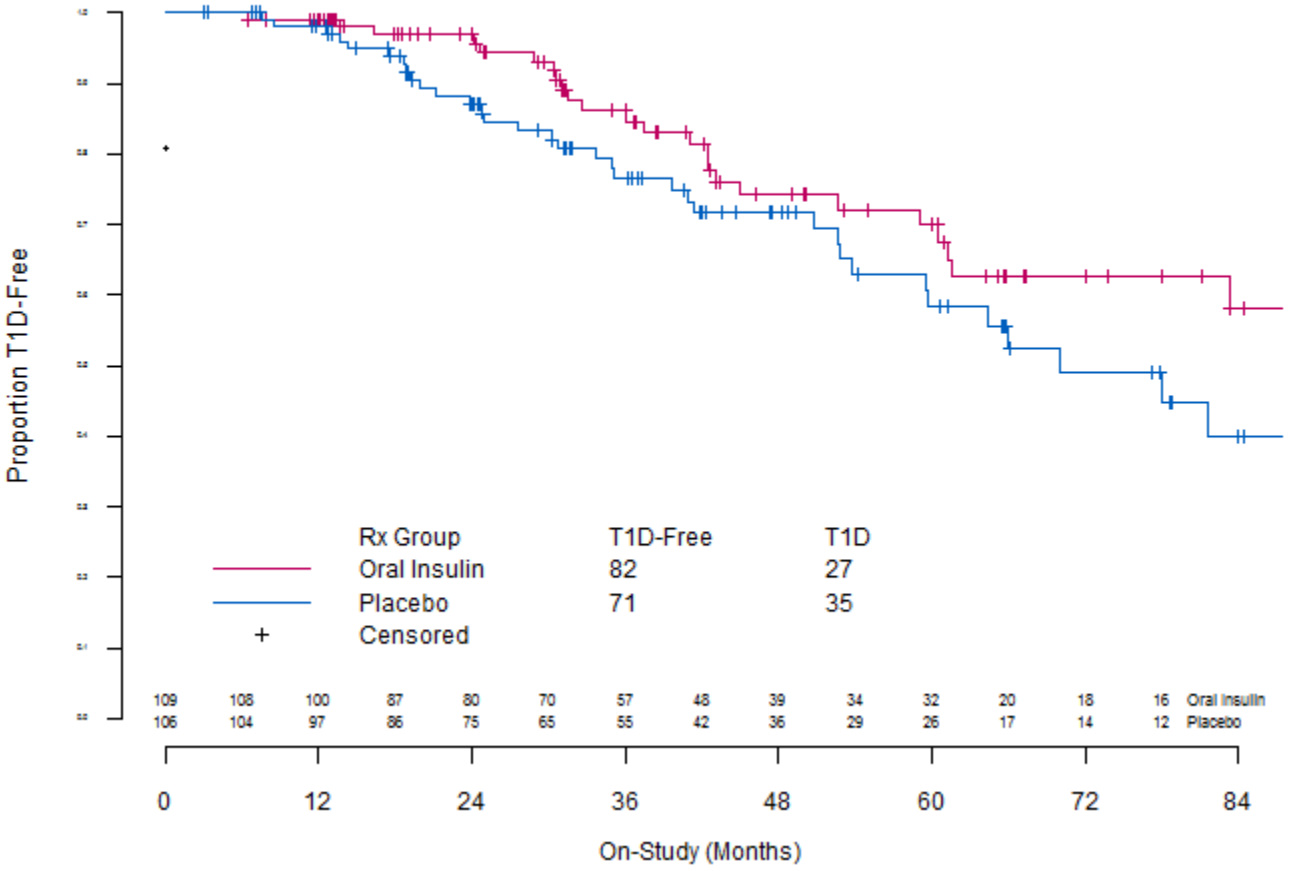
All participants were requested to return unused pills to the clinic at each visit. Therefore, at our disposal were the number of pills issued, the number of pills returned and the date this accounting took place. From these data, we computed the average proportion of pills "taken" based on the number of pills that should have been ingested for the interval of time between visits (approximately 6 months). The required dosage was one pill per day, and so perfect adherence (a proportion of 1 or 100%) would be when the number of pills 'taken' is equal to the number of days in which the pills were in the participant's possession between consecutive pill accounting clinic visits. Where there were missing adherence data (46 in the primary stratum), we imputed the pill adherence proportion 3 ways in an attempt to determine the treatment effect during the first 24 months on study: 1) no pills after the last pill report, 2) half the proportion they had taken in their last report, 3) the same proportion of pills as they had taken in their last report. To quantify the functional relationship between adherence and risk, a LOWESS (locally weighted regression and smoothing scatterplot) curve was fitted to the Cox model (with adjustment) residuals as a function of adherence for each treatment group separately. Greater adherence was correlated with less risk of T1D in both treatment groups in the range of 0.8 and larger regardless of the imputation method used. Analysis of adherence was conducted both quantitatively (Cox model) and qualitatively (comparing the 'good' adherence subgroup by treatment). Unless otherwise specified in the results, imputation option 2 was employed because it represents a compromise between the other two extreme options.

Effect of Adherence

In a per protocol analysis of the primary stratum which included participants with 85% or more adherence with treatment (n=215), the annualized rate of diabetes was 6.9% with oral insulin and 9.7% with placebo (hazard ratio 0.688 (95% CI 0, 1.04), p=.06). In examining Kaplan-Meier curves for the primary stratum that included participants with varying degrees of adherence, in more adherent participants there was separation between the oral insulin and placebo groups during the first 24 months after randomization. Therefore, in an analysis of the first 24 months' follow-up of adherent participants in the primary stratum, a protective effect was observed with less progression to diabetes as compared to placebo - annualized rate of diabetes was 2.4% with oral insulin and 6.9% with placebo (hazard ratio 0.348 (95% CI 0, 0.855) p=0.016 (Figure S1).

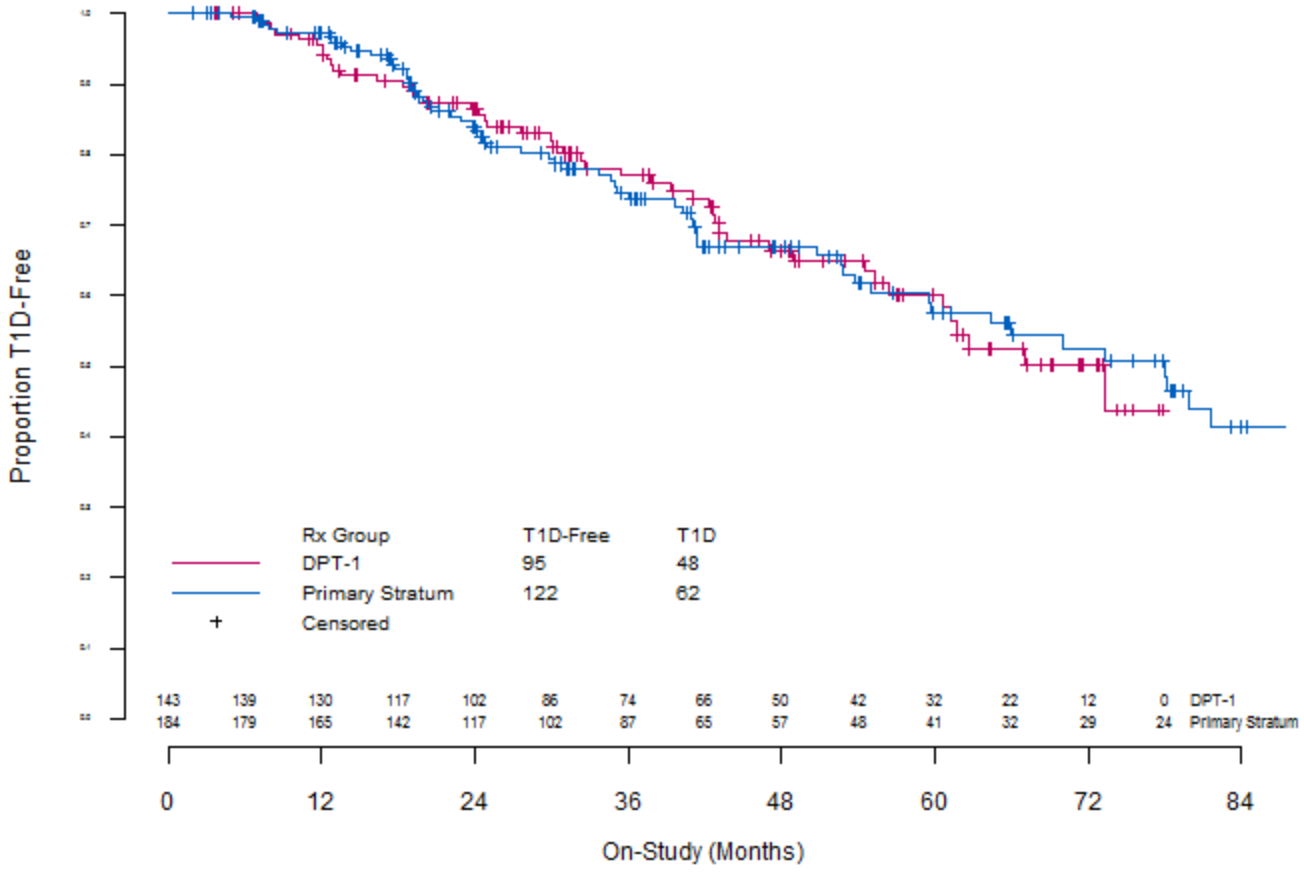
eFigure 1. Proportion of Study Individuals Remaining Type 1 Diabetes Free

Proportion of study individuals remaining type 1 diabetes free as a function of follow-up for individuals in the primary stratum who have ≥ 85% study drug adherence. Quartiles of time to diabetes in months = 20.8, 36.7, 61 for oral insulin and 19.5, 36.7, 59.7 for placebo.



eFigure 2

Proportion of study individuals remaining type 1 diabetes free as a function of follow-up comparing the placebo treated groups from the DPT-1 study and the primary stratum of the TrialNet oral insulin study. Quartiles of time to diabetes in months = 21.7, 37.7, 56.7 for oral insulin and 18.9, 32.7, 54.4 for placebo.



Adverse Events:

For the adverse effects analysis we included the entire cohort since there is no reason to believe that adverse event risk differed by stratum. All adverse effects are included in the tables below regardless of the assigned causality assigned. Adverse events of severity level 1 were not required to be reported although on occasion they were and this monitoring stipulation is accommodated in the tables below.

The number of participants by their worst (highest grade) adverse event and treatment group are displayed in the table below. Note categories 0 and 1 were grouped. A Wilcoxon test was employed to test the severity distribution by treatment group; the test was not significant (p = 0.10, 1-tail test).

eTable 1. Adverse Events by Severity Grade

Severity (Grade)	Treatment Group	
	Oral Insulin No. of participants (%)	Placebo No. of participants (%)
0/1	133 (47.0)	144 (52.0)
2	114 (40.3)	104 (37.5)
3	35 (12.4)	29 (10.5)
4	1 (0.4)	0 (0)
5	0 (0.0)	0 (0.0)
Total	283 (100.0)	277 (100.0)

* 0 represents no reported events

The number of events and number of participants experiencing any of the various types of adverse events by treatment group are displayed in the table below. Only grades 2 and higher are counted as adverse events. A series of Mantel-Haenszel chi-squared test (1-tail) were applied to each 2x2 table formed by whether or not the type of adverse events was experienced by the participant and the treatment group assigned. Only one category was statistically significant: Muscular-Skeletal/Soft Tissue with p =0.005 (1-tail test). The next closest to significance were Allergy/Immunology and Surgery/Intra-operative Injury with a significance level of 0.18 (1-tail).

eTable 2. Adverse Events by Category

	Oral Insulin		Placebo	
Adverse Effect Category	No. of events	No. of participants N= 283 (%)	No. of events	No. of participants N = 278 (%)
Ocular/Visual	4	4 (1.4)	4	4 (1.4)
Infection	134	67 (23.7)	120	62 (22.4)
Pulmonary/Upper Respiratory	51	30 (10.6)	37	30 (10.8)
Endocrine	18	18 (6.4)	12	12 (4.3)
Musculoskeletal/Soft Tissue	45	38 (13.4)	20	18 (6.5)
Allergy/Immunology	18	17 (6.0)	11	11 (4.0)
Dermatology/Skin	29	25 (8.8)	20	18 (6.5)
Cardiac Arrhythmia	2	2 (0.7)	1	1 (0.4)
Gastrointestinal	30	28 (9.9)	34	25 (9.0)
Constitutional Symptoms	13	10 (3.5)	18	12 (4.3)
Surgery/Intra-Operative Injury	7	7 (2.5)	3	3 (1.1)
Neurology	15	13 (4.6)	17	12 (4.3)
Auditory/Ear	14	12 (4.2)	15	11 (4.0)
Hemorrhage/Bleeding	2	2 (0.7)	1	1 (0.4)
Metabolic/Laboratory	0	0 (0.0)	4	4 (1.4)
Pain	14	11 (3.9)	11	11 (4)
Syndromes	4	4 (1.4)	2	2 (0.7)
Renal/Genitourinary	1	1 (0.4)	5	3 (1.1)
Blood/Bone Marrow	1	1 (0.4)	2	2 (0.7)
Hepatobiliary/Pancreas	3	2 (0.7)	0	0 (0.0)
Sexual/Reproductive Function	1	1 (0.4)	2	2 (0.7)
Cardiac General	0	0 (0.0)	0	0 (0.0)
Lymphatics	1	1 (0.4)	1	1 (0.4)
Total Events	407	---	340	---