SOP-NOD-0002 Allocation of Study Subjects to Treatment Groups

STANDARD OPERATING PROCEDURE
Pre-clinical Consortium on Combination Therapies for Type I Diabetes

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Title: Allocation of Study Subjects to Treatment Groups

INTRODUCTION/PURPOSE

The goal of this study is to determine the efficacy of anti-CD20 monoclonal antibody therapy (alone), oral insulin (alone), or the combination of anti-CD20 plus oral insulin to reverse hyperglycemia in NOD mice with recent onset autoimmune diabetes.

The purpose of this Standard Operating Procedure is to describe the methods by which study participants will be allocated to treatment groups.

DEFINITIONS

Day 1: The day of initiation of treatment. Study enrollment and treatment initiation will begin the same day as the second consecutive confirmatory hyperglycemic reading.

Treatment Group	Category	n	Treatment
A	Negative Control	18	Insulin pellet (subcutaneous implant). One LinBit insulin implant to be implanted the same day as the second consecutive confirmatory hyperglycemic reading (d 1). Second insulin pellet to be implanted once the first is expended (day 10-18). Oral diluents (oral gavage, twice weekly for 6 weeks = 12 total administrations) begining the first Tuesday or Thursday following onset. Isotype control antibody (10 mg/kg IP injection on days 1, 2, 3, and 4).
B	Test	18	Insulin pellet (subcutaneous implant). One LinBit insulin implant to be implanted the same day as the second consecutive confirmatory hyperglycemic reading (d 1). Second insulin pellet to be implanted once the first is expended (day 10-18). Oral insulin (oral gavage, twice weekly for 6 weeks = 12 total

			administrations) begining the first Tuesday or Thursday following onset.
C	Test	18	Insulin pellet (subcutaneous implant). One LinBit insulin implant to be implanted the same day as the second consecutive confirmatory hyperglycemic reading (d 1). Second insulin pellet to be implanted once the first is expended (day 10-18). Anti-CD20 monoclonal antibody (10 mg/kg IP injection on days 1, 2, 3, and 4).
D	Test	18	Insulin pellet (subcutaneous implant). One LinBit insulin implant to be implanted the same day as the second consecutive confirmatory hyperglycemic reading (d 1). Second insulin pellet to be implanted once the first is expended (day 10-18). Oral insulin (oral gavage, twice weekly for 6 weeks = 12 total administrations) begining the first Tuesday or Thursday following onset. Anti-CD20 monoclonal antibody (10 mg/kg IP injection on days 1, 2, 3, and 4).
E	Test	18	Insulin pellet (subcutaneous implant). One LinBit insulin implant to be implanted the same day as the second consecutive confirmatory hyperglycemic reading (d 1). Second insulin pellet to be implanted once the first is expended (day 10-18). Anti-CD20 monoclonal antibody (10 mg/kg IP on day 1) Delayed oral insulin (oral gavage, twice weekly for 6 weeks beginning on day 21 = 12 total administrations running through day 63)
F	Positive Control for Diabetes Reversal	10	Anti-CD3 monoclonal antibody (5 micrograms on days 1-5 = 5 total administrations)
G	Test	18	Oral insulin (oral gavage, twice weekly for 6 weeks = 12 total administrations) begining the first Tuesday or Thursday following onset. Anti-CD20 monoclonal antibody (10 mg/kg IP injection on days 1, 2, 3, and 4).

PROCEDURES

1. Subjects that have been entered into the study based on the methods and criteria described in *SOP-NOD-0001: Subject Identification, Inclusion/Exclusion Criteria, and Study Enrollment* will be allocated to treatment groups the same day as the second consecutive confirmatory hyperglycemic reading.

2. Subjects will be allocated sequentially to groups A (main control group), D (core treatment group), and F (positive control group) before enrolling the other groups until each of these groups contains 5 animals.

3. Following enrollment of 5 animals into Groups A (main control group), D (core treatment group), and F (positive control group), an interim data analysis will be performed to identify a positive signal in group D.

4. If an early positive signal (first 5 animals) is seen in group D, the study can continue to enroll mice in the other groups. If there is no signal from the core treatment group, the steering committee can then decide whether to test the treatment with delayed insulin (group E) or other groups. If a positive signal is seen at one or two of the sites, but not the others, the study will continue and later on can address the discrepancy in efficacy between sites.

5. Once the remaining groups are opened for enrollment, subjects will be allocated to groups sequentially. For example, the first subject will be allocated to Group A, the second to Group B, etc. Once subjects have been allocated to Groups A through G, then the next subject will be allocated to Group A and the entire process repeated until all groups have 10 subjects entered.

6. Once 10 subjects have been entered into each group, Group F will be complete and the remaining allocations will be performed sequentially, skipping Group F, until all groups are complete.

DOCUMENTATION TO BE MAINTAINED

REFERENCES TO OTHER APPLICABLE SOPS

SOP-NOD-0001.00: Subject Identification, Inclusion/Exclusion Criteria, and Study Enrollment

REFERENCES

Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG (2010) Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. PLoS Biol 8(6): e1000412. oi:10.1371/journal.pbio.1000412

van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, et al. (2010) Can Animal Models of Disease Reliably Inform Human Studies? PLoS Med 7(3): e1000245. doi:10.1371/journal.pmed.1000245

FORMS/ATTACHMENTS

REVISION HISTORY

Effective Date	Revision	Author	Description of Changes

7/26/2011		A. Posgai	Changed the day that subjects should be allocated to treatment groups after initial blood glucose reading from the third day to the *second* day.
8/17/11	.01	T Kupfer	Addition of definition of day 1 and modification to the procedure for group allocation. First, 5 animals to be allocated to groups A, D & F. Interim data analysis at this point will determine how the study will proceed.
9/1/11	.02	T Kupfer	Change of dosing for anti-CD20 and isotype control antibody therapies from days 1, 21, and 42 to days 1-4.