ONLINE ONLY APPENDIX

Failure to Preserve beta-cell function with Mycophenolate Mofetil and Daclizumab Combined Therapy in patients with new onset Type 1 Diabetes

Peter A. Gottlieb, MD, Scott Quinlan, MS, Heidi Krause-Steinrauf, MS, Carla J. Greenbaum, MD, Darrell M. Wilson, MD, Henry Rodriguez, MD, Desmond A. Schatz, MD, Antoinette M. Moran, MD, John M. Lachin, ScD, Jay S. Skyler, MD for the Type 1 Diabetes TrialNet MMF/DZB Study Group.

The Type 1 Diabetes TrialNet Mycophenolate Mofetil-Daclizumab (MMF-DZB) Study Group

Steering Committee: Jay S. Skyler (University of Miami Diabetes Research Institute), Chairman; Mark Anderson (University of California San Francisco), Dorothy Becker (University of Pittsburgh), Christophe Benoist (Joslin Diabetes Center), Penelope Bingley (University of Bristol), Emanuele Bosi (San Raffaele Hospital), H. Peter Chase (University of Colorado Barbara Davis Center for Childhood Diabetes), Michael Clare-Salzler (University of Florida), Peter Colman (Walter and Eliza Hall Institute of Medical Research), George S. Eisenbarth (University of Colorado Barbara Davis Center for Childhood Diabetes), C. Garrison Fathman (Stanford University), Stephen Gitelman (University of California San Francisco), Robin Goland (Columbia University), Peter Gottlieb (University of Colorado Barbara Davis Center for Childhood Diabetes), Gilman Grave (NICHD), Carla Greenbaum (Benaroya Research Institute), Leonard Harrison (Walter and Eliza Hall Institute of Medical Research), Kevan Herold (Yale University), Richard Insel (Juvenile Diabetes Research Foundation), Francine Kaufman (Childrens Hospital Los Angeles), Jeffrey P. Krischer (University of South Florida), Ellen Leschek (NIDDK), Jeffrey Mahon (University of Western Ontario), Jennifer Marks (University of Miami Diabetes Research Institute), Antoinette Moran (University of Minnesota), Kirsti Nanto-Salonen (Hospital District of Southwest Finland), Gerald Nepom (Benaroya Research Institute), Tihamer Orban (Joslin Diabetes Center), Jerry P. Palmer (University of Washington), Robertson Parkman (Childrens Hospital Los Angeles), Mark Peakman (Guy’s, King’s, and St. Thomas’ School of Medicine), Mark Pescovitz (Indiana University), John Peyman (NIAID), Alberto Pugliese (University of Miami Diabetes Research Institute), Philip Raskin (University of Texas Southwestern Medical School), Henry Rodriguez (Indiana University), Desmond Schatz (University of Florida), Robert Sherwin (Yale University), Mark Siegelman (University of Texas Southwestern Medical School), Olli Simell (Hospital District of Southwest Finland), Massimo Trucco (University of Pittsburgh), John Wagner (University of Minnesota), Diane Wherrett (University of Toronto), Darrell Wilson (Stanford University), William Winter (University of Florida), Anette Ziegler (Institut für Diabetesforschung), Judith Fradkin (NIDDK, ex-officio).

Past Members: Jeffrey Bluestone (University of Miami Diabetes Research Institute), Philip Raskin (University of Texas Southwestern Medical School), Henry Rodriguez (Indiana University), Desmond Schatz (University of Florida), Robert Sherwin (Yale University), Mark Siegelman (University of Texas Southwestern Medical School), Olli Simell (Hospital District of Southwest Finland), Massimo Trucco (University of Pittsburgh), John Wagner (University of Minnesota), Diane Wherrett (University of Toronto), Darrell Wilson (Stanford University), William Winter (University of Florida), Anette Ziegler (Institut für Diabetesforschung), Judith Fradkin (NIDDK, ex-officio).
Minnesota), Stanley Jordan (Cedars-Sinai Medical Center), John M. Lachin (George Washington University), John Ridge (NIAID).

Executive Committee: Jay S. Skyler, Carla J. Greenbaum, Jeffrey P. Krischer, Ellen Leschek, John Peyman, Lisa Rafkin-Mervis (University of Miami Diabetes Research Institute), Peter Savage (NIDDK), Lisa Spain (NIDDK). Past Members: Catherine Cowie, Mary Foulkes (George Washington University), Heidi Krause-Steinrauf (George Washington University), John M. Lachin, Saul Malozowski (NIDDK), John Ridge, Stephanie J. Zafonte (George Washington University).

For the MMF-DZB Study, the following individuals were involved:

Chairman's Office: Jay S. Skyler, Carla J. Greenbaum, Norma S. Kenyon, Lisa Rafkin-Mervis, Jay M. Sosenko

Coordinating Center (at the time of the study): John M. Lachin, Heidi Krause-Steinrauf, Scott Quinlan, Kimberly Hess, Erica Raiden

NIDDK Staff: Judith Fradkin, Ellen Leschek, Peter Savage, Lisa Spain, Past Member: Saul Malozowski

Data Safety and Monitoring Board: Emily Blumberg (University of Pennsylvania), Chair; Jonathan Braun (University of California Los Angeles), Lori Laffel (Joslin Diabetes Center), Ali Naji (University of Pennsylvania), Jorn Nerup (University of Copenhagen), Trevor Orchard (University of Pittsburgh), Anastasios Tsiatis (North Carolina State University), Robert Veatch (Georgetown University), Dennis Wallace (Research Triangle Institute). Past Members: Ake Lernmark (Lund University), Bernard Lo (University of California San Francisco), Herman Mitchell (Rho Inc.), Michael Steffes (University of Minnesota), Bernard Zinman (University of Toronto).

Infectious Disease Safety Committee: Brett Loechelt (Children's National Medical Center) (Medical Monitor), Lindsey Baden (Harvard University), Michael Green (University of Pittsburgh), Adriana Weinberg (University of Colorado)

Laboratory Directors: George S. Eisenbarth, Santica Marcovina (University of Washington), Jerry P. Palmer, Adriana Weinberg, William Winter, Liping Yu (University of Colorado Barbara Davis Center for Childhood Diabetes)

Protocol Advisory Committee: Peter A. Gottlieb (Chair), H. Peter Chase, Sherrie Harris, Norma Kenyon, Heidi Krause-Steinrauf, John Lachin, Mark Pescovitz, Henry Rodriguez, Darrell Wilson; Ex-officio: Carla Greenbaum, John M. Lachin, Ellen Leschek, Jay S. Skyler; Scott Quinlan (liaison).

Clinical Center Staff involved in this Protocol:
This Online Only Appendix presents supplemental material not contained in the published manuscript.
Figure A1: Enrollment, Randomization and Follow-up of Study Participants.
Table A1. Summary of Grade 2+ Adverse Events of Interest by Treatment Group. Only events that occurred in 2 or more subjects within a treatment group are shown.

| Event                  | MMF+DZB (N=41) | MMF-alone (N=31) | Placebo Control (N=42) | p-value* |
|------------------------|----------------|------------------|------------------------|----------|
|                        | # Events # (%) Subjects w/ Event | # Events # (%) Subjects w/ Event | # Events # (%) Subjects w/ Event |          |
| Infection              | 59 26 (63.4)   | 40 17 (54.8)     | 47 24 (57.1)           | 0.765    |
| Conjunctivitis         | 0 0 (0)        | 1 1 (3.2)        | 4 4 (9.5)              | 0.075    |
| Elevated EBV viral load** | 7 5 (12.2)   | 9 1 (3.2)        | 3 2 (4.8)              | 0.344    |
| HSV, GU                | 1 1 (2.4)      | 2 1 (3.2)        | 0 0 (0)                | 0.530    |
| HSV, oral              | 5 4 (9.8)      | 4 3 (9.7)        | 1 1 (2.4)              | 0.307    |
| Sinusitis              | 3 3 (7.3)      | 2 2 (6.4)        | 5 1 (2.4)              | 0.579    |
| Sore throat            | 13 10 (24.4)   | 7 5 (16.1)       | 12 11 (26.2)           | 0.613    |
| URI                    | 19 11 (26.8)   | 8 7 (22.6)       | 16 11 (26.2)           | 0.927    |
| UTI                    | 2 2 (4.9)      | 2 1 (3.2)        | 1 1 (2.4)              | 0.836    |
| Wart                   | 2 2 (4.9)      | 0 0 (0)          | 1 1 (2.4)              | 0.631    |
| GI Toxicity            | 13 7 (17.1)    | 12 9 (29.0)      | 12 9 (21.4)            | 0.487    |
| Diarrhea               | 7 6 (14.6)     | 5 4 (12.9)       | 5 5 (11.9)             | 0.941    |
| Emesis                 | 5 4 (9.8)      | 6 5 (16.1)       | 2 2 (4.8)              | 0.222    |
| Nausea                 | 1 1 (2.4)      | 0 0 (0)          | 3 3 (7.1)              | 0.450    |
| Hematologic            | 9 7 (17.1)     | 14 9 (29.0)      | 9 6 (14.3)             | 0.288    |
| Leukopenia             | 1 1 (2.4)      | 4 3 (9.7)        | 0 0 (0)                | 0.064    |
| Lymphopenia            | 0 0 (0)        | 2 2 (6.4)        | 0 0 (0)                | 0.072    |
| Neutropenia            | 8 7 (17.1)     | 8 6 (19.4)       | 9 6 (14.3)             | 0.860    |
| Miscellaneous          | 45 22 (53.7)   | 25 10 (32.3)     | 29 16 (38.1)           | 0.147    |
| Cough                  | 6 6 (14.6)     | 1 1 (3.2)        | 2 2 (4.8)              | 0.187    |
| Elevated liver enzymes| 7 4 (9.8)      | 0 0 (0)          | 0 0 (0)                | 0.13     |
| Headache               | 4 4 (9.8)      | 5 1 (3.2)        | 2 2 (4.8)              | 0.551    |
| Hyperglycemia          | 4 3 (7.3)      | 3 3 (9.7)        | 4 3 (7.1)              | 0.914    |
| Hypoglycemia           | 19 11 (26.8)   | 13 7 (22.6)      | 18 8 (19.1)            | 0.692    |
| Pain                   | 2 2 (4.9)      | 1 1 (3.2)        | 1 1 (2.4)              | 0.836    |
| Condition                      | DZB alone | DZB + GS6177 | Placebo alone | Placebo + GS6177 | p-value |
|--------------------------------|-----------|---------------|---------------|------------------|---------|
| Mood alteration                | 3         | 2 (4.9)       | 2             | 2 (6.4)          | 1.000   |
| Serious                        | 19        | 14 (34.2)     | 9             | 5 (16.1)         | 0.007   |
| Cataract                       | 2         | 1 (2.4)       | 0             | 0 (0)            | 0.632   |
| Elevated liver enzymes        | 2         | 2 (4.9)       | 0             | 0 (0)            | 0.200   |
| Hyperglycemia                  | 1         | 1 (2.4)       | 0             | 0 (0)            | 0.778   |
| Neutropenia                    | 3         | 3 (7.3)       | 1             | 1 (3.2)          | 0.530   |

* p-value is based on two-sided Fisher’s exact test
** > 10,000 DNA copies/ml

Six additional serious adverse events occurred in the DZB alone group (emesis, fracture, hypoglycemia, 2 neutropenia, and poor diabetes control) not included in the table above.