FINAL REPORT
Volume 1 of 5

Testing Facility Study No. EBA00066

Sponsor Study No. P00012-05-05

BG00012: An 11-Month Toxicity Study of BG00012 Administered by the Oral (Capsule) Route to Dogs with a 1-Month Recovery Period

TESTING FACILITY:

Charles River Laboratories
Preclinical Services
640 North Elizabeth Street
Spencerville, OH 45887

SPONSOR:

Biogen Idec, Inc.
14 Cambridge Center
Cambridge, MA 02142

April 9, 2007

1. COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice (GLP) regulations as described by the FDA (21 CFR Part 58); and the Organisation for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice, C(97)186/Final with the following exception(s):

Characterization and stability analyses of the bulk test article were conducted in compliance with GMP regulations.

Toxicokinetic evaluation and reporting and histopathology peer review, conducted by the Sponsor, were not in complete compliance with GLP regulations.

The lack of GLP compliance of the above portions of the study was not considered to impact the validity of the study results.

Mark A. Morse 4/9/07

Mark A. Morse, Ph.D., DABT Date
Study Director
Charles River Laboratories
Preclinical Services

2. QUALITY ASSURANCE STATEMENT

This study has been inspected by the Quality Assurance Unit to assure conformance with the Good Laboratory Practice (GLP) regulations promulgated by the FDA (21 CFR Part 58); and OECD Principles of Good Laboratory Practice, C(97)186/Final. Reports were submitted in accordance with Standard Operating Procedures as follows:

QA INSPECTION DATES

		Date Findings Submitted to:	
Dates of Inspection	Phase(s) Inspected	Study Director	Study Director Management
09/19/05	Protocol Review	10/11/05	10/11/05
10/13/05	Protocol Amendment Review	11/23/05	11/23/05
10/16/05	Data Audit	10/21/05	10/21/05
10/18/05	Dose Preparation	10/21/05	10/21/05
10/18/05	Dosing	11/23/05	11/23/05
10/18/05	Blood Collection – Bioanalytical (4 hour)	10/21/05	10/21/05
10/18/05	Bioanalytical Sample Processing (4 hour)	10/21/05	10/21/05
10/18/05	Blood Collection – Bioanalytical (4.5 hour)	11/23/05	11/23/05
10/18/05	Bioanalytical Sample Processing (4.5 hour)	11/23/05	11/23/05
10/24/05	Bioanalytical Sample Shipping	11/23/05	11/23/05
11/21/05	Protocol Amendment Review	04/14/06	04/14/06
12/16/05	Data Audit	12/20/05	12/20/05
12/19/05, 12/29/05	Data Audit	01/26/06	01/26/06
12/30/05, 01/03/06	Data Audit	02/07/06	02/07/06
01/04/06, 02/07/06	Data Audit	02/10/06	02/10/06
01/13/06	Blood Collection – Clinical Pathology	01/13/06	01/13/06
01/13/06	Hematology	01/13/06	01/13/06
01/23/06	Dose Preparation	01/26/06	01/26/06
01/26/06	Dosing	01/26/06	01/26/06
02/07/06, 02/22/06	Data Audit	11/01/06	11/01/06
03/07/06, 03/08/06	Data Audit	03/08/06	03/08/06
04/11/06, 04/17/06, 04/22/06, 10/30/06, 11/09/06, 11/10/06	Data Audit	11/10/06	11/10/06
04/14/06	Blood Collection – Clinical Pathology	04/14/06	04/14/06
04/14/06	Clinical Chemistry	04/14/06	04/14/06
04/17/06	Blood Collection – Bioanalytical	04/17/06	04/17/06
04/17/06	Bioanalytical Sample Processing	04/17/06	04/17/06
04/24/06	Bioanalytical Sample Shipping	04/27/06	04/27/06
04/24/06	Dosing	04/27/06	04/27/06
05/06/06, 05/15/06	Data Audit	05/15/06	05/15/06
05/08/06	Dose Preparation	05/08/06	05/08/06
05/09/06, 05/12/06	Protocol Amendment Review	05/12/06	05/12/06
05/20/06	Data Audit	05/20/06	05/20/06
06/02/06, 06/05/06, 10/09/06	Data Audit	10/09/06	10/09/06
06/27/06	Protocol Amendment Review	06/27/06	06/27/06
07/17/06	Blood Collection – Bioanalytical	07/17/06	07/17/06
07/17/06	Bioanalytical Sample Processing	07/17/06	07/17/06

Dates of Inspection	Phase(s) Inspected	Date Findings Submitted to: Study Director	Study Director Management
07/21/06	ECG's	07/21/06	07/21/06
07/21/06	Blood Pressures	07/21/06	07/21/06
07/25/06	Dosing	07/25/06	07/25/06
08/01/06, 08/16/06, 08/17/06, 09/12/06, 09/13/06	Data Audit	09/13/06	09/13/06
08/29/06	Dose Preparation	08/31/06	08/31/06
09/01/06, 09/05/06, 09/13/06, 09/28/06	Data Audit	09/28/06	09/28/06
09/06/06, 09/07/06, 10/02/06, 10/03/06	Data Audit	10/03/06	10/03/06
09/08/06	Protocol Amendment Review	09/08/06	09/08/06
09/12/06	Blood Collection – Bioanalytical	09/12/06	09/12/06
09/12/06	Bioanalytical Sample Processing	09/12/06	09/12/06
09/14/06, 09/15/06	Urinalysis	09/15/06	09/15/06
09/14/06	Blood Collection – Clinical Pathology	09/15/06	09/15/06
09/14/06	Necropsy	09/15/06	09/15/06
09/14/06	Organ Weights	09/15/06	09/15/06
09/18/06	Bioanalytical Sample Shipping	09/18/06	09/18/06
10/06/06, 10/09/06	Data Audit	10/09/06	10/09/06
10/11/06	Data Audit	10/11/06	10/11/06
10/19/06, 10/23/06	Data Audit	10/23/06	10/23/06
10/24/06, 10/27/06	Data Audit	10/27/06	10/27/06
10/25/06, 10/31/06, 11/08/06	Data Audit	11/08/06	11/08/06
10/26/06	Data Audit	10/26/06	10/26/06
10/30/06, 10/31/06, 11/09/06, 11/10/06	Data Audit	11/10/06	11/10/06
01/26/07	Data Audit	01/26/07	01/26/07
03/08/07, 03/09/07	Draft Report Review	03/09/07	03/09/07
03/12/07	Data Audit	03/15/07	03/15/07
04/03/07, 04/06/07	Final Report Review	04/06/07	04/06/07

4. SUMMARY

The purpose of this study was to evaluate the potential toxicity and toxicokinetics of the test article, BG00012, when administered in two divided doses daily for a minimum of 11 months by oral (capsule) administration followed by a 1-month recovery period. The study design was as follows:

Experimental Design

Group No.	No. of Main Study (Recovery) Animals		Test Material	Dose Level (mg/kg)	Necropsy Day (Recovery)
	Males	Females			
1	4 (2)	4 (2)	BG12 placebo [redacted]	75/50[a] (0 mg/kg test article)	332/333 (365)
2	4 (2)	4 (2)	BG12[redacted]	5	332/333 (365)
3	4 (2)	4 (2)	BG12[redacted]	25	332/333 (365)
4	4 (2)	4 (2)	BG12[redacted]	75/50[a]	332/333 (365)

[a]Beginning on Day 7, due to adverse signs noted in Group 4 animals, the dose level for Groups 1 and 4 was decreased to 50 mg/kg.

The following variables and end points were evaluated in this study: clinical signs, physical examinations, body weights, body weight changes, food consumption, ophthalmology, cardiology, blood pressure, clinical pathology (hematology, clinical chemistry, and urinalysis), toxicokinetics, gross necropsy, organ weights, and histopathology.

Results:

There were no test article-related mortalities. All animals survived until scheduled euthanasia.

Test article-related clinical signs during the dosing phase were largely restricted to gastrointestinal disturbances such as an increased incidence of soft stools in 75/50 mg/kg/day animals, an increased incidence of mucoid stools in 25 mg/kg/day animals and 75/50 mg/kg/day animals, an increased incidence of vomitus, primarily in 75/50 mg/kg/day animals, and no feces/few feces in 75/50 mg/kg/day males. In addition, ocular discharge was observed in some 75/50 mg/kg/day animals. There were no relevant clinical signs observed during the recovery phase.

Profound test article-related effects on body weight, body weight gain, and food consumption were observed in 75/50 mg/kg/day animals during the dosing phase. Animals in the 75/50 mg/kg/day dose group lost over 15% of their initial body weight over the first several weeks and had reduced body weight gains compared to controls throughout the dosing phase due to test article-induced inappetence. Because of this inappetence, dietary supplements including Nutrical and Science Diet® were offered to 75/50 mg/kg/day dogs. Males and females in the 5 mg/kg/day and 25 mg/kg/day dose groups had body weight gains and food consumption values more comparable to controls during the dosing phase. Where present, reductions in body weight or body weight gain in 25 mg/kg/day or 75/50 mg/kg/day animals occurred within the first five

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