TABLE 25.1 Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Blinded Study Treatment With BG00012/Placebo

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	$>3\times$ ULN	The Investigator should repeat the test as soon as possible. If retest value confirms AST or ALT $>3\times$ ULN, the study treatment must be withheld. If the value remains $>3\times$ ULN for greater or equal to 4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment**
Creatinine	$>1.2\times$ ULN	The Investigator should repeat the test as soon as possible. If retest value confirms that creatinine $>1.2\times$ ULN, the study treatment must be withheld. If the value remains $>1.2\times$ ULN for $\geq$4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment**
White blood cell (WBC)	$<2000/mm^3$	The Investigator should repeat the test as soon as possible. If retest value confirms that WBC $<2000/mm^3$, the study treatment must be withheld. If the value remains $<2000/mm^3$ for greater or equal to 4 weeks after discontinuation of study treatment, then the subject **must *permanently* discontinue study treatment**
Urine cytology	Positive	Urine cytology must be performed on any subject who has hematuria of unknown etiology on two consecutive visits. If urine cytology is positive, then the subject **must *permanently* discontinue study treatment**

An exemplary account of instructions for dose withholding or permanent discontinuation, in response to abnormal laboratory values, is provided in a Clinical Study Protocol used in a clinical trial on multiple sclerosis (45,46). The Protocol provided brief instructions and a table (see Table 25.1). The instructions read, "Dosing Interruption for Abnormal Laboratory Values ... treatment with [study drug or] placebo must be temporarily withheld when any of the following laboratory values meet the threshold limits defined in Table 11.2-1." This table is reproduced here, as Table 25.1.

Table 25.1 provides instructions for dose withholding and also for permanent discontinuation. The emphasis (bold) is in the original table. The term "ULN" means, upper limit of normal. The terms AST (SGOT) and ALT (SGPT) refer to enzymes (aminotransferases) that are released by the liver into the serum, where elevated serum levels indicate liver damage. In the table, the term "BG00012" is the study drug, which is also known as dimethyl fumarate.

e. FDA's Warning Letter on Dose Modification

On occasion, the FDA issues Warning Letters to the Sponsor when there are repeated and uncorrected violations of instructions in the Clinical Study Protocol, or of other

[45]A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis. EUDRA CT NO: 2006-003697-10. DATE: 09 January 2008. Protocol No. 109MS302. Version 4.

[46]The Clinical Study Protocol is a supplement to, Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. New Engl. J. Med. 2012;367:1087–97.