completed a given series of treatments. The instructions for dose increase read:

> [D]ose escalation is not permitted during the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of LDK378 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of LDK378, he or she must have received the lower dose for at least 4 cycles of therapy without a drug-related toxicity of CTCAE grade 2:: 2.

2. *Dose Modifications in Clinical Study Protocol for Anemia*

This concerns a Clinical Study Protocol that provided instructions for *increasing* or *decreasing* doses based on the efficacy of the drug. The study drug was *darbepoetin* (129). These instructions were keyed to efficacy values, not to any adverse events associated with the drug. To emphasize this point, even though the Protocol provided instructions for decreasing the dose, these were keyed with efficacy values, not with any drug-induced toxicity.

The drug was darbepoetin for treating anemia, and the efficacy was determined by blood values for hemoglobin (Hb), as well as the rate of increase over the course of time of blood hemoglobin. Instructions were provided by a table (Table 2.1). These instructions referred to prefilled syringes. The syringes contained the study drug in the amounts of 10, 15, 20, 30, 40, 50, 60, 80, 100, 150, 200, and 300 μg.

TABLE 2.1 Dose Modification Instructions for Clinical Trial on Darbepoetin for Anemia[a]

Hemoglobin (g/dL)	Hb Rate of Rise (g/dL/2 weeks)	Instruction
Under 12.2	Under 0.5	Increase to next higher prefilled syringe
Under 12.2	0.5–1.0	Maintain dose
Under 12.2	Greater than or equal to 1.0	Decrease to next lower prefilled syringe
12.5–13.5	Under 0.5	Maintain dose
12.5–13.5	0.5–1.0	Maintain dose
12.5–13.5	Greater than or equal to 1.0	Decrease to next lower prefilled syringe

[a]*Instructions slightly modified from table in Clinical Study Protocol of Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. New Engl. J. Med. 2010;363:1146–55.*

3. *Dose Modifications in Clinical Study Protocol for Cushing's Disease*

A Clinical Study Protocol (130) regarding a drug for treating Cushing's disease provided instructions for dose reduction and dose escalation, where the instructions identified specific adverse events. These adverse events included hypoadrenalism, as defined by serum cortisol levels. The instructions also stated the amount of the dose reduction, and how to monitor the adverse event after the physician had imposed the dose reduction:

> The dose may be reduced at any time in steps of 300 μg b.i.d. in case of intolerance (1200 μg b.i.d. to 900 μg b.i.d., 900 μg b.i.d. to 600 μg b.i.d., 600 μg b.i.d. to 300 μg b.i.d.). The lowest dose that should be administered is 300 μg b.i.d. However, a lower dose (such as 150 μg b.i.d.) may be allowed as long as efficacy is maintained; otherwise, the patient should be discontinued from the study. Dose reductions are required for the following criteria: Evidence of hypoadrenalism: defined as an early morning (between 8 and 10 AM) serum cortisol <3 μg/dL and a UFC measurement $<$ LLN or symptoms suggestive of hypoadrenalism (e.g. postural hypotension, nausea, and abdominal pain) and a UFC measurement $<$ LLN … [d]ose reductions are to be performed as follows: The dose will be reduced by 300 μg b.i.d. for one week. If the AE improves to grade ≤ 2 within one week, increase dose by 300 μg b.i.d.

[129]Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. New Engl. J. Med. 2010;363:1146–55.

[130]Colao A, Petersenn S, Newell-Price J, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. New Engl. J. Med. 2012;366:914–24.