The Clinical Study Protocol stated that (158):

> **Dose selection.** The selection of starting dose was based on the rat STD_{10} from the 4-week GLP study (50 mg/kg/day). Expressing 50 mg/kg in the rat based on body surface area is equivalent to 300 mg/m^2. Applying a safety factor of 10, the starting dose in humans would be 1/10th of the STD_{10} in rats or 1/10th of 300 mg/m^2 = 30.0 mg/m^2. Since 1/10th of the STD_{10} in rat is below the HNSTD in the monkey (30 mg/kg or 360 mg/m^2), this dose is expected to be well tolerated by the monkey. Therefore, the rat is considered an appropriate species. Thus, based on an average BSA of 1.73 m^2, the recommended safe flat starting dose of LDK378 [study drug] is 51.9 mg/patient (50 mg/patient).
>
> The human efficacious dose was estimated by tumor kinetic PK/PD modeling. By fitting plasma LDK378 [study drug] PK and tumor regression dynamics in two xenograft models, key tumor regression parameters (tumor doubling time) and drug effect (IC50 and Hill coefficient) can be estimated. Target exposure of tumor inhibition ranging from … stable disease … to 90% regression … can be calculated and considered potentially therapeutic in patients. Derived from tumor kinetic PK/PD modeling, plasma AUC_{0-24} values ranging from 3000 to 12408 ng*hr/mL are considered potentially therapeutic target exposures in patients and were used to estimate the potentially therapeutic dose range humans. The following equation was employed: Dose (human) = (CL/F)* (AUC_{tau}), where AUC_{tau} corresponds to the exposure at steady-state leading to the desired pharmacologic effects, CL represent the predicted human clearance, and F is the human absolute bioavailability and estimated to be 0.7. Therefore, the human efficacious dose range is estimated to be 120 to 480 mg/day, based on exposures associated with *in vivo* tumor growth inhibition, i.e., tumor stasis to 90% tumor regression in the … rat models.

2. *Drug for a Disease of the Intestinal Mucosa (Crohn's Disease)*

An interesting nuance for the technique for extrapolating from mouse dose to human dose, comes from a clinical trial on a drug used to treat an autoimmune disease (colitis) of the gut. The Clinical Study Protocol explained (159):

> After careful consideration of the appropriate basis for extrapolating efficacious doses in mice to humans, a judgment was made that this should be based on the intestinal mucosal surface area. The primary rationale for this is that the product, when delivered orally, is only minimally absorbed systemically and is essentially delivered topically to the intestinal epithelium. Therefore, the human-equivalent efficacious dosage was calculated as described … [t]he surface area of the colon and terminal ileum of the mice used in the above experiments is 947.5 mm^2 … so, it is 265 fold smaller than the corresponding human surface area, which is approximately 251,000 mm^2. Since the therapeutic dose in mice with colitis was 0.125 mg/mouse, we established the dose to use in humans by multiplying this value for 265. The calculated dose (33 mg).

VI. ORIGIN OF DRUGS THAT ARE BIOSIMILARS

"Biosimilars" refers to a class of drug called biologicals. Biologicals include antibodies, viruses, vaccines, serums, blood products, and polypeptides (160). Polypeptides that are biosimilars are those made by expression in living cells, and do not include polypeptides made by organic synthesis. The term biosimilars is

[158]Oncology Clinical Trial Protocol CLDK378X2101. A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK); August 19, 2010.

[159]A phase II multicenter, randomized, double-blind, controlled vs placebo, dosefinding study on the efficacy and safety of GED-0301, in patients with active Crohn's disease (Ileo-Colitis). Protocol: GED-301-01-11. EUDRACT NUMBER 2011-002640-27.

[160]Abraham J. Developing oncology biosimilars: an essential approach for the future. Semin. Oncol. 2013;40 (Suppl. 1):S5–24.