

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**103948/0**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

## Review of the Clinical Pharmacokinetics for BLA 99-0786, CAMPATH-1H

CAMPATH-1H is a humanized antibody to CD52 antigen that is expressed on a human peripheral blood lymphocytes, monocytes, and macrophages. The precise function of CD52 is not established and may participate in cell adhesion, host defense and/or cell proliferation. Effector mechanisms exerted by CAMPATH-1H include ADCC and complement fixation. Due to its lymphocyte depleting effect, CAMPATH-1H was developed for the treatment of CLL as a third-line therapy in patients failing fludarabine therapy.

The pharmacokinetics of CAMPATH-1H were investigated in 4 multicenter, open-label studies in patients. These studies were 3 Phase 3 studies: 125-001-C-91 (001), 125-002-C-91 (002) and 125-003-C-91 (003) and 1 Phase 2 study – 125-005-C92 (005). Study 125-001-C-91 used a dosing regimen of 3 times weekly at dosages of 2.5, 8, 25 or 80 mg; study 125-002-C-91 a dosing regimen of 1 time weekly at dosages of 7.5, 24, 75, or 240 mg; study 125-003-C-91 used a dosing regimen of 5 times weekly at dosages of 0.5, 5 or 50 mg. In study 125-002-C-91, patients ultimately given 75 or 240 mg were initially given either 7.5 or 24 mg doses at week 1. In study 125-005-C92 (005), doses of 30 mg were given 3 times weekly for 6 to 12 weeks by iv or sc routes of administration.

In studies 125-001-C-91, 125-003-C-91 and 125-005-C-92, serum samples of CAMPATH-1H were measured immediately before and at the end of each infusion for the first 4 weeks of treatment, every 1 to 2 weeks during treatment, and monthly until below detectable levels in studies 125-001-C-91, 125-003-C-91; in study 125-005-C-92, serum samples were collected at 28 days post-treatment. In study 125-005-C-92 125-002-C-91, a complete pharmacokinetic profile was established at the first week and fourth week of treatment; additionally, pre-, mid-, and post-infusion at 0.25, 0.5, 1, 2, 4, 6, 8, 24, 72 and 168 hours after dosing. In studies 125-001-C-91, 125-003-C-91 and 125-005-C-92, no formal pharmacokinetic analysis of the data for parameters such as clearance was computed due to the limited nature of the sampling, which is primarily peak and trough data. However, a rough estimate of half-life was obtained from the data from study 125-005-C-92 from 30 of 52 patients, as this was the dosing regimen selected for use in the pivotal trial CAM211.

The following table highlights some of the values derived from study 002 as listed in the sponsor's submission. The full table is found as Table 8.3.2.2.5B vol. 3.6 of 3.79 volumes. Generally, C<sub>max</sub> increases with repeated dosing through week 3 of the study and C<sub>max</sub> appears proportional to dose.

Dose, mg	Week	Number pts	C <sub>max</sub> , ug/ml
2.5	1	2	0.6 ± 0.1
	2	3	0.68 ± 0.3
	3	4	0.7 ± 0.5
	4	6	0.6 ± 0.6
8	1	3	1.6 ± 0.8
	2	6	2.4 ± 1.8
	3	9	1.9 ± 1.4
	4	8	2.7 ± 1.9
25	1	12	3.7 ± 2.5
	2	14	4.6 ± 4.6
	3	9	7.6 ± 4.4
	4	8	8.7 ± 5
80	1	11	8.4 ± 11.7
	2	14	17.8 ± 22.9
	3	14	23.2 ± 25.8
	4	11	22.7 ± 24.4

Table of C<sub>max</sub> as means and SD from study 001.

The following table highlights some of the values derived from study 002 as listed in the sponsor's submission. The full table is found as Table 8.3.2.2.3A vol. 3.6 of 3.79 volumes. Accumulation is observed between the first and fourth infusions along with an increase in Cmax and AUC/Dose for both 7.5 and 24 mg doses. Additionally, AUC is not proportional (nonlinear) to doses between 7.5 and 24 mg on the first infusion. By the fourth infusion nonlinearity was observed in the highest dose only; this is likely due to the removal of malignant cells that participate in the disposition of CAMPATH-1H. The great extent of variability is expressed in the relatively large standard deviations associated with the pharmacokinetic values.

Dose, mg	Number pts	AUC, ug-hr/ml	Cmax, ug/ml	AUC/Dose
7.5 infusion 1	28	12.5 ± 15	0.62 ± 0.43	2.2 ± 2.4
24 infusion 1	28	76 ± 53	3.8 ± 2	4.1 ± 3.3
7.5 infusion 4	8	28.8 ± 27.3	1.2 ± 0.8	5.4 ± 6.6
24 infusion 4	9	149.4 ± 170.8	5.1 ± 2.8	7.7 ± 6.9
75 infusion 4	17	442.8 ± 490	12 ± 6	5.2 ± 5.3
240 infusion 4	7	2408 ± 1804	54 ± 28	17.2 ± 12.8

Summary table of pharmacokinetic values as means ± SD from study 002.

The following table summarizes some pharmacokinetic values derived from study 003 as listed in the sponsor's submission. The full table is found as Table 8.3.2.2.6B vol. 3.6 of 3.79 volumes. A considerable degree of interpatient variability was observed in the data set. Mean Cmax exhibited a tendency to increase with repeated dosing that was increased by increases in doses.

Dose, mg	Week	Number pts	Cmax, ug/ml
0.5	1	5	0.04 ± 0.05
	2	5	0.1 ± 0.18
	3	5	0.1 ± 0.2
	4	4	0.2 ± 0.2
5	1	23	0.9 ± 0.8
	2	23	1.7 ± 1.3
	3	21	1.8 ± 1.6
	4	18	1.8 ± 1.6
50	1	5	9.5 ± 4.7
	2	4	27.6 ± 7.9
	3	4	38 ± 5.9
	4	3	47.9 ± 8.3

Table of CAMPATH-1H Cmax (means ± SD) from study 003

The following table highlights some pharmacokinetic values derived from study 005 and listed in the sponsor's submission. The full table is found as Table 8.3.2.2.4A vol. 3.6 of 3.79 volumes. Mean values for peak and trough generally rise from week 1 to week 8. The data for NHL patients suggests a tendency for more accumulation with repeated dosing as compared to patients with CLL. This is mostly likely due to differences in disease burden and is consistent with a greater number of malignant cells in patients with CLL. Since malignant cells participate in the clearance of CAMPATH-1H, higher numbers of cells reduces both peak and trough values. An inverse relationship was observed between the duration of dosing and levels of circulating lymphocytes. No formal relationship was determined between pharmacokinetic values and circulating lymphocyte counts. A substantial difference in the relative magnitude of the peak serum concentration was observed between patients with levels of absolute lymphocyte counts less than or equal to  $30 \times 10^9/L$  versus those patients with  $ALC > 30 \times 10^9/L$  prior to week 6 of treatment. The greatest difference was observed at week 2 with a relative difference of approximately 7 fold in CAMPATH levels. Similar changes occurred in regards to trough concentrations.

Disease	Week	Number	Peak to Trough	Trough, ug/ml	Peak, ug/ml
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		patients	ratio		
P-CLL	1	12	12	0.2	2.4
	2	18	4	1.2	4.6
	3	20	3	2.1	6.4
	4	17	3	2.6	7.1
	5	16	2	3.3	7.4
	6	11	3	2	6.6
	7	7	4	2.1	8.1
	8	7	3	2.1	7.1
NHL	1	26	7	.8	5.6
	2	24	2	2.3	8.2
	3	18	3	4.1	9.7
	4	18	2	5	10.4
	5	13	2	5.4	11.2
	6	10	3	5.7	14.7
	7	6	3	3.2	8.3
	8	3	2	3.4	7.9
PU- CLL	1	1	6	.1	0.6
	2	5	10	.6	6
	3	5	5	1.3	6.1
	4	5	4	2.3	8.4
	5	4	4	2.0	8.3
	6	2	2	2.8	5.8
	7	3	4	2.2	8.4
	8	3	2	4.8	8.7

Table of mean trough and peak levels for CAMPATH-1H from study 005. P = previously treated CLL; PU = previously untreated.

The following conclusions may be drawn from the available data on the pharmacokinetics of CAMPATH.

1. An inverse relationship exists between disease burden and pharmacokinetic parameters such as C<sub>max</sub> and AUC as malignant cells participate in the removal of CAMPATH-1H.
2. Increases in both C<sub>max</sub> and C<sub>min</sub> occur with repeated dosing and this effect is extenuated by increases in dose and directly proportional to the frequency of dosing. This is likely to be a consequence of the half-life of CAMPATH-1H in relationship to the dosing interval. Although not rigorously estimated the half-life is thought to be about 30 to 40 hours. Steady-state levels are achieved at approximately 6 weeks of repeated dosing and are a consequence of the dosing interval and disease burden as well as half-life.
3. Plasma levels of CAMPATH-1H exhibited a high degree of inter-patient variability.

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