

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103948/0

PHARMACOLOGY REVIEW

APR 27 2001

Nonclinical Pharmacology, Pharmacokinetics and Toxicology Review of CAMPATH

BLA: 99-0786

Product: CAMPATH, 30 mg iv 3 times a week for a maximum of 12 weeks

Sponsor: L & I Partners, LP

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 was developed for the treatment of CLL as a third -line therapy in patients failing fludarabine therapy.

Toxicology

The following four studies were cited in support of the BLA as the primary basis for assessing nonclinical toxicity. These studies were conducted by _____ using nonhuman primates. Among the various laboratory animals examined, it was found that only a subgroup of cynomolgus monkeys expressed CD52 on their lymphocytes. In these monkeys, the affinity of CAMPATH-1H for CD52 is about 16-fold less as compared to humans.

1. A preliminary study of the toxicity, pharmacodynamics, and pharmacokinetics of CAMPATH-1H in the cynomolgus monkey following intravenous administration at 0.1, 1 and 3 mg/kg. BPAT/90/0063, _____
2. A preliminary study of the pharmacodynamics, and pharmacokinetics of CAMPATH-1H in the cynomolgus monkey following subcutaneous administration at 1, 2, and 3 mg/kg. BPAT/90/0110, _____
3. A preliminary toxicity study with CAMPATH-1H by intravenous and subcutaneous injection in cynomolgus monkeys. TTDR/90/0036/4. _____
4. Study on the cardiovascular and respiratory effects of CAMPATH-1H by intravenous injection in anesthetized cynomolgus monkeys. BPHP/92/0039 (/162/911385)

Toxicity studies that were conducted in cynomolgus monkeys used the intravenous (iv) and subcutaneous routes of administration. Doses studied ranged from 0.1 to 3 mg/kg. A safety pharmacology study was conducted to elucidate the cardiovascular and respiratory effects of CAMPATH-1H following a single iv dose from 3 to 30 mg/kg. Several toxicity studies re-enrolled monkeys and essentially created a repeated dose escalation study. The findings of these studies is likely confounded by the repeated exposure and development of antibodies to CAMPATH-1H.

After iv dosing of 1 or 3 mg/kg lymphocytopenia was observed in all animals. Lymphopenia was not observed at 0.1 mg/kg. In responding animals, nadirs were observed between 8 and 48 hours post-injection; recovery was observed approximately 2 to 5 weeks post exposure. At 1 or 3 mg/kg variable changes in platelet count and slight increases in reticulocyte counts were found. No macroscopic or microscopic changes were recorded after treatment with CAMPATH-1H. Similar toxicity findings occurred after sc injection of CAMPATH-1H at all doses studied (1, 2, and 3 mg/kg). Times to nadir were 48 to 10 days post dosing with recovery occurring approximately 3 to 6 weeks later. Repeated doses of CAMPATH-1H were given to different groups of cynomolgus monkeys in a dose escalation scheme in conjunction with two different durations of exposure (study TTDR/90/0039). Groups of monkey and their routes of administration were as follows - group 1 (N=1/sex) iv control (normal saline) for 30 days of injection; group 2 (N=1/sex) iv for 14 days; group 3 (N=1/sex) iv for 30 days; group 4(N=2 males) sc for 14 days and group 5 (N=2 males) sc for 30 days). For monkeys in groups 1, 3 and 5 the dose was 0 or 1 mg/kg on days 1 to 7 and 1.5 mg/kg days 11 to 14; 2 mg/kg days 11 to 14 and 3 mg/kg days 15 to 30. Lymphopenia after repeat dosing was more pronounced as compared to a single iv or sc dose and reached a nadir of 1% of

predose counts or less; additionally a neutropenia was observed with repeated dosing. Both the lymphocytopenia and neutropenia were reversible upon cessation of dosing.

No major changes in cardiovascular or respiratory function were found at doses of 3 mg/kg, but at doses of 10 and 30 mg/kg a moderate to severe dose-related hypotension followed dosing that persisted for 3.5 hours accompanied by a slight tachycardia. One monkey doses at 30 mg/kg dies at about 6 hours after injection after demonstrating marked hypotension, tachycardia, and hyperpnea. Several other physiological changes occurred in male monkeys given 10 or 30 mg/kg which may reflect the changes in cardiovascular and respiratory function.

No reproductive, developmental or genotoxicity studies were performed with CAMPATH-1H.

Cross Reactivity Studies

Studies were conducted to characterize the cross reactivity of CAMPATH-1H with a range of human tissues. CAMPATH-1H binds to B and T cell lymphocytes, monocytes, thymocytes, and macrophages. In bone marrow, binding is greater on mature B cells in comparison to immature B cells. A small percentage of neutrophils, less than 5%, also bind to CAMPATH-1H, however, binding or interaction does not occur with red blood cells, platelets, or hematopoietic stem cells. Cross-reactivity of the antigen binding region of CAMPATH-1H to the epididymis, sperm, seminal vesicle and skin does occur. No cross-reactivity was found to the following tissues: vaginal, uterium, ovarian, cervical, breast, thymus, submandibular gland, spleen, parathyroid, pancreas, smooth muscle, skeletal muscle, and cardiac muscle, lung, kidney, cancellous bone, bladder, aorta, prostate, esophagus, stomach, small and large intestine. Nonspecific binding was found to cells of the cerebrum, cerebellum and spinal cord that is possibly associated with microglia. In the adrenal gland and arterial blood vessels cross-reactivity was associated with small peripheral nerve fibers.

Biodistribution

A biodistribution study was conducted in CD-1 mice bearing CHO-10/D4 tumors that were transfected with the CD52 gene. Comparative levels of exposure were determined for the blood, spleen and tumor at 7, 24, and 48 hours after iv dosing. Data were expressed as a percentage of injected dose per gram of tissue; corrections were made for capillary blood content of the tissues. The highest levels were found in the spleen and liver both a 7 and 24 hours. The tumor, spleen and liver contained at 7 hours 5.8, 32.8% and 20.2% and at 24 hours 8.8, 18.1% and 13.6%. At 48 hours, levels dropped to 6.2% and 8.5% as compared to 20.7% for radioactivity in the tumor tissue.

Pharmacokinetics

Pharmacokinetic data were derived from toxicokinetic information taken from toxicity studies of cynomolgus monkeys and a single study of 35-S-labeled CAMPATH-1H. Toxicokinetics were assessed in the following studies: BPAT/90/0063, BPAT/ 90/0110, BPHP 92/0039.

The bioavailability of CAMPATH was 47% after a sc dose. A summary of the pharmacokinetic data are provided as an attached appendix that documents selected pharmacokinetic endpoints as reported in various toxicity studies for CAMPATH. Due to the nature of the analysis and the limitations of the data, the pharmacokinetic endpoints reported below should be considered highly preliminary. For example, in study BPHP/92/0039, animals experienced significant cardiovascular effects that are likely to have significantly influenced the pharmacokinetic data. Additionally, anti-CAMPATH-1H antibodies were observed in animals at various times and may have altered pharmacokinetic relationships. No line listings of individual pharmacokinetic data were available for review.

Martin D. Green 4-25-01
Martin D. Green, Ph.D.

Patricia Keegan 4-27-01

Appendix 1.

Study	Dose, mg/kg	T1/2 β , h	Cl, ml/h/kg	Vd, L/kg
BPAT/90/0063, iv	0.1 to 3	233 \pm 15	0.25 \pm 0.05	0.09 \pm 0.02
BPAT/90/0110, sc	1 to 3	-----	0.58 \pm 0.22	0.13 \pm 0.05
BPHP/92/0039, iv	3	11.5	-----	-----
BPHP/92/0039, iv	10	17.9 \pm 6.4	-----	-----
BPHP/92/0039, iv	30	17.6 \pm 12.6	-----	-----

Summary table of pharmacokinetic data.