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August 23, 1984

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UCLA School of Medicine
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Los Angeles, CA 90024

RE: Treatment of Herpes Virus Infections with Zovirax® (Acyclovir) or Condyloma Acuminata with Wellferon® (Human Lymphoblastoid Interferon) In Patients with Unexplained Lymphadenopathy Syndrome

Dear Dr. Gottlieb:

Thank you for sending your statement of investigator form and updated curriculum vitae. This documentation will be processed for the registration of your study in the late fall.

I shall anticipate receiving your budget proposal sometime in the near future. Please feel free to call me at any time with questions or recommendations for the study. Give my regards to Drs. Hardy and Wolfe.

Sincerely,

Pamela

Pamela Britt-Harrington, R.N.
Immunology Section
Department of Clinical Investigation

THZA/84/3401
PBH/sw/D3/03



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August 1, 1984

Michael Gottlieb, M.D.
Assistant Professor of Medicine
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10833 Le Conte Avenue
Los Angeles, CA 90024

RE: Treatment of Herpes Virus Infections with Zovirax® (Acyclovir) or
Condyloma Acuminata with Wellferon® (Human Lymphoblastoid) in Patients
with Unexplained Lymphadenopathy Syndrome

Dear Dr. Gottlieb:

It was a pleasure meeting with you and your associates during my most recent visit to UCLA on July 25th, 1984. Thank you for the extended time you spent discussing the protocol and data collection form with me. Pursuant to our conversation at that time, I now come back to you with follow-up to questions that were raised:

1. Eligibility criteria (3.1.1) (pg. 18 in protocol)
#4. Symptoms of weight loss, night sweats, low grade fever, or prominent fatigue will be omitted.
2. A total of thirty patients will be enrolled in the study. When thirty patients have been assessed, we can evaluate the need to extend the study to answer additional questions about this patient population.

Also, as we discussed, IRB submission of the protocol with the patient consent form needs immediate attention so we can meet our tentative target initiation date of November 1984. Secondly, begin to put together your budget proposal briefly describing personnel time commitments on a percentage basis. I shall anticipate receiving the various documentation required for the study in the next several weeks.

This project is most fascinating and I look forward to working with Drs. Wolfe, Hardy and you over the next year. Please do not hesitate to call me at 919-248-3171 if you have any questions regarding plans for initiation of the study.

Best regards,

Pamela

Pamela Britt-Harrington, R.N.
Immunology Section
Department of Clinical Investigation

vp/1/6/2
THZA/84/3204

TREATMENT OF HERPES VIRUS INFECTIONS
WITH ZOVIRAX® (ACYCLOVIR) OR CONDYLOMA ACUMINATA
WITH WELLFERON® (HUMAN LYMPHOBLASTOID INTERFERON)
IN PATIENTS WITH UNEXPLAINED LYMPHADENOPATHY SYNDROME

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Immunology Section
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DRAFT: August 13, 1984

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WELLFERON® OR ZOVIRAX® FOR VIRAL INFECTIONS
IN UNEXPLAINED LYMPHADENOPATHY SYNDROME

1.0 OBJECTIVES

- 1.1 To determine response patterns of condyloma acuminata of LAS patients to 6 weeks of treatment with human lymphoblastoid interferon (WELLFERON).
- 1.2 To characterize response of herpes virus infections in LAS patients to oral acyclovir (ZOVIRAX) administration.
- 1.3 To determine the tolerance and toxicity of acyclovir or human lymphoblastoid interferon in patients with LAS.
- 1.4 To measure response rates and patterns of recurrent/resistant condyloma acuminata or recurrent herpes virus infections to a second six-week course of human lymphoblastoid interferon or acyclovir, respectively.
- 1.5 To determine the effectiveness of combined acyclovir and interferon treatment for disease that does not respond to initial acyclovir or interferon therapy alone.
- 1.6 To study the molecular virology of herpes viruses and condyloma acuminata which do and do not respond to acyclovir or interferon therapy.

2.0 BACKGROUND AND RATIONALE

2.1 Prolonged Unexplained Lymphadenopathy Syndrome

The acquired immunodeficiency syndrome (AIDS) is defined as biopsy-confirmed Kaposi's Sarcoma and/or the occurrence of one or more life-threatening opportunistic infections in persons with no previously documented immune deficiency (1). Patients with AIDS have prominent defects in cell-mediated immunity. Clinical manifestations may include anergy, marked reduction in T-helper cell numbers, inversion of T-helper/T-suppressor cell ratios, depressed mitogen and antigen responses and depressed natural killer cell activity (2, 3). Retrospective studies and analyses of newly occurring cases have demonstrated the existence of major groups at high risk of acquiring AIDS. These are: homosexual and bisexual men, intravenous drug abusers,

persons born in Haiti and now living in the U.S., patients with hemophilia, and recipients of blood transfusions.

The first report of AIDS was in the Spring of 1981. As of December, 1983, 3000 cases that meet the current definition of AIDS had been reported by physicians and health departments in the U.S. (4). Of these reported cases, 1283 or 43% of patients are known to have died. One of the striking epidemiologic features of AIDS is the age factor; 90% of reported patients are between 20 and 49 years old. Although the rate of increase of diagnosed cases appeared lower during the last half of 1983, this may reflect a longer lag-time in reporting cases to local, state, and national health agencies.

Simultaneous with the AIDS epidemic, a syndrome of prolonged unexplained generalized lymphadenopathy (LAS) was recognized in the same population groups at increased risk for AIDS (5). These patients exhibit lymphadenopathy which may be associated with low grade fevers, night sweats, weight loss, and/or fatigue. Lymph node biopsies reveal follicular hyperplasia (6). Peripheral blood T-helper/T-suppressor ratios are typically reduced in some cases due to reduced numbers of T-suppressor/cytotoxic cells. These patients may have an unusual acid-labile form of human leukocyte, or alpha, interferon in their serum (7). Persons with LAS and immune deficiency appear to be at increased risk for development of AIDS (8).

One of the major problems for AIDS patients is the high number of opportunistic and virus infections, often occurring concomitantly. Virus infections, in particular Cytomegalovirus and Epstein-Barr virus, occur in nearly 100% of these patients. Due to suppressed immunity, herpes simplex infections of the genital or perianal area can become quite severe and/or chronic. Volberding and colleagues (9) have reported that 17/20 patients, in their initial trial with human IFN- α_2 , developed herpes simplex infections during the course of study. Another virus-associated disease, condyloma acuminata, was observed in 7/20 patients entered in that study (9). Because virus infections

pose such a problem for these patients, intervention with antiviral agents at early stages of disease development seems logical for prevention of severe infections and possible viral dissemination.

Acyclovir (ZOVIRAX®) is a potent antiviral that has been marketed for intravenous or topical application as treatment of mucocutaneous herpes simplex virus infections. In addition, an oral capsule formulation is being evaluated extensively in on-going clinical trials. Human lymphoblastoid interferon (WELLFERON®) is a highly purified preparation of a mixture of alpha interferons and presently is under clinical development for viral and oncologic indications. A pilot study and multicenter Phase II study have demonstrated that this interferon is effective in treating severe resistant/recurrent condyloma acuminata in males and females. It is the purpose of the present study to employ these two agents, at doses and schedules known to be effective, for the treatment of these two types of viral diseases in LAS patients. ZOVIRAX will be given orally to patients with herpes virus infections and WELLFERON will be administered subcutaneously to patients with condyloma acuminata of the genital area, perianal or rectal mucosa.

2.2 Interferons

2.2.1 Description

Interferon was the term used originally for an inducible cellular factor which protected eukaryotic cells against influenza virus infection (10). Today it is known that this agent is a protein secreted by cells in response to viral or other stimuli (e.g., mitogens, antigens) and that it elicits a number of biological responses. Some of the properties associated with interferon, in addition to antiviral activity, include immunomodulatory and antiproliferative effects.

2.2.2 Biologic Properties

Three major types of interferons have been identified and differ in their molecular weight, antigenicity, stability and other biochemical properties. Current nomenclature refers to human interferons as alpha (HuIFN- α), beta (HuIFN- β) and gamma (HuIFN- γ) which were formerly leukocyte, fibroblast and immune interferons, respectively. Cells induced to make interferon by viral or other stimuli commonly synthesize more than one type but a preparation is usually identified by the predominant component. The following table outlines the known human interferons:

NOMENCLATURE OF HUMAN INTERFERONS

<u>Current</u>	<u>Former</u>	<u>No. of Genes</u>	<u>Chromosome</u>	<u>Properties</u>
HuIFN- α	Leukocyte	12-13	9	Acid-stable; Virus-induced.
HuIFN- β	Fibroblast	1	9	Acid-stable; Virus-induced.
HuIFN- γ	Immune	1	12	Acid-labile; Mitogen-induced.

The numerous bacteria-derived human alpha subtypes differ in their antiviral properties (11) and they are distinct from HuIFN- β and HuIFN- γ . The identification of these multiple interferons with different biological properties has led to the identification of what is now referred to as "the interferon system" (12).

Interferon for clinical evaluation may be produced from blood leukocytes, from cell lines of fibroblasts or lymphoblasts, all stimulated with virus, or by recombinant DNA techniques. The interferon to be administered in this study, WELLFERON®, is purified from supernatants of cultures of human lymphoblastoid cells, Namalwa, after Sendai virus stimulation (See Section 4.1). The

purification process results in a product containing multiple subtypes of HuIFN- α . Its chemical, physical, immunologic and biologic properties closely resemble those of the most widely used native interferon, the leukocyte interferon prepared by the Finnish Transfusion Service from buffy coat cells of donated blood.

2.2.3 Antiviral Activities of Interferons

A substantial database documenting in vitro and in vivo antiviral properties of interferons has been reviewed comprehensively in other sources (13, 14). In brief, studies performed principally in vitro have revealed that:

- a. most cell types can produce an interfering substance and can respond to it by the development of an antiviral state.
- b. the substance is not virucidal but rather confers protection by inducing expression of certain cellular genes.
- c. the antiviral effect is not virus specific.
- d. exquisitely small amounts are required for protection.
- e. the protection of cells may show some degree of species specificity.

Interferon is also important in the control of viral infections in vivo. The appearance and level of interferon correlate with host recovery and that correlation is better than for other elements of host defense systems (15). Its role was more clearly established when anti-interferon antibody was shown to compromise host recovery from viral infection (16). Numerous therapeutic models have been developed in which the application of exogenous interferon or the induction of endogenous interferon modulates viral infection. Consistent with the in vitro findings, interferon is active against a wide spectrum of viruses in a variety of animal hosts.

2.2.4 Interferon in the Treatment of Human Viral Diseases

Although interferons were identified originally by their antiviral nature, clinical evaluation in viral diseases has been limited. Appropriate studies have been hampered by the practical problems of limited supplies and the fact that interferon is most effective as an antiviral when administered prophylactically. A growing body of evidence from studies carried out at relatively low doses is demonstrating that exogenous interferon can produce antiviral effects in man.

Some of the most significant responses to interferon in virus-associated disease have been reported in patients with laryngeal papillomas. These epithelioproliferative growths afflict the larynx and airways of both children and adults and contain viral DNA from a unique subtype of human papilloma virus, HPV-11. Four reported studies utilizing leukocyte-derived interferon have shown that systemic administration of low doses of interferon causes regression and/or growth control of these warty lesions (17, 18, 19, 20).

Hepatitis B virus has been treated with alpha or beta interferon in several studies. Weimar et al. (21) reported daily treatment with 12 Mu and weekly maintenance at 50% dose decrements produced a decrease only in DNA polymerase levels. Work by Merigan and colleagues has addressed the question of combined therapy in the treatment of chronic hepatitis. Studies employing adenine arabinoside, leukocyte interferon or a combination of these have shown that multiple cycles of the two agents were most effective in eradicating serum DNA polymerase activity (22). Treated patients also had improved liver biopsies and reduced serum transaminase levels (23).

A variety of herpesvirus infections has also been treated with interferon. In cutaneous varicella zoster, disease improvement has been observed at the higher

doses tested (24). Disease dissemination, new vesicle formation, acute pain, post-herpetic neuralgia and visceral complications were all reduced. However, short-term therapy (48 hours) at the same dose resulted in only modest effects on the symptoms observed (25). In a separate study, 44 immunocompromised children with cancer were treated with leukocyte interferon resulting in a diminished spread of infection in the skin and visceral complications (26). The value of prophylactic interferon against HSV-1 infections was demonstrated in patients undergoing trigeminal nerve surgery (27). Both virus shedding and the incidence of recurrent herpes labialis was reduced. Topical application of interferon showed limited efficacy in herpetic dendritic keratitis but significantly reduced healing time and virus shedding when combined with debridement (28) or trifluorothymidine (29). Immunocompromised homograft recipients are at high risk for viral infection and many develop HSV and CMV infections. Interferon therapy post-transplant has shown limited efficacy (30); whereas, IFN prophylaxis for 14 weeks in 20 transplant recipients resulted in significant reduction of clinical signs of CMV infection (31).

2.3 Acyclovir

2.3.1 Description

Acyclovir [9-(2-hydroxy ethoxy methyl) guanine] is an acyclic purine nucleoside analog that is a potent inhibitor of herpes simplex virus (HSV), types 1 and 2, replication. This compound is highly selective in inhibiting viral enzyme and has extremely low toxicity for host cells. A very substantial database has been established on the mechanism of action of this agent and preclinical testing of safety and efficacy. The very high therapeutic index of this compound can be explained by a number of differences between cellular

and virus-encoded enzymes (32). Experimental work has shown that:

- a. herpesvirus-encoded thymidine kinase phosphorylates acyclovir; cellular thymidine kinase does not.
- b. HSV-infected cells contain 40-100 times greater amounts of acyclo-GTP than uninfected cells.
- c. viral polymerases are more sensitive to acyclo-GTP inhibition than cellular DNA polymerases.
- d. acyclo-GTP is a much better template for viral polymerases.
- e. viral DNA polymerase has a 50-fold greater affinity for acyclo-GMP-terminated template.

The sum total of these selective inhibitions is a 300 to 3000-fold difference in the toxicity of acyclovir to herpes viruses and to the cell (32).

2.3.2 Antiviral Properties of Acyclovir

Numerous in vitro studies have demonstrated acyclovir's activity against HSV, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella zoster virus (HZV), and other herpes virus infections. Studies in nonhuman primates, guinea pigs, rabbits, and mice have documented its antiviral activities in vivo. The results of such experimentation have been reviewed thoroughly in the proceedings of a recent symposium (33). In brief, pre-clinical animal studies have demonstrated that:

- a. topical application is effective against cutaneous herpes simplex in guinea pigs.
- b. genital herpes virus type 2 infection of mice and guinea pigs can be treated successfully by topical therapy.
- c. oral or subcutaneous administration at 10 mg/kg is effective against herpetic encephalitis in mice.
- d. application of 1, 2, or 3% ointment is effective in treating herpetic keratitis in rabbits.

- e. intravenous or intramuscular dosing effectively inhibits similar varicella virus infection.
- f. murine cytomegalovirus is exquisitely sensitive to acyclovir both in vitro and in vivo.

These results coupled with extensive toxicologic studies in animals have confirmed the high selectivity of acyclovir for herpes viruses and its low toxicity for uninfected cells.

2.3.3 Use of Acyclovir in Humans

Acyclovir has been approved for intravenous and topical use for treatment of mucocutaneous herpes simplex virus infections. Intravenously administered acyclovir has shown clinical efficacy in a number of studies of patients with herpes simplex and varicella zoster virus infections (33). At present, an oral capsule formulation is being studied extensively in clinical trials. This orally administered form has demonstrated clinical efficacy in first-episode and recurrent genital herpes simplex infections (34, 35). Its efficacy for other mucocutaneous herpes infections, varicella zoster, and Epstein-Barr virus infections is currently under investigation.

2.4 Interferon in Treatment of Condyloma Acuminata

Condyloma acuminata, or genital warts, are benign fibro-epithelial tumors of suspected viral etiology. Viral particles in condyloma tissue were demonstrated first by electron microscopy and were classified as members of the papillomavirus group (36, 37). Human papilloma viruses (HPV) are a heterogeneous group consisting of at least eighteen distinct types (38, 39). Types 1, 2, 3, 4 and 7 have been associated with benign skin warts. The type found in condyloma tissue is designated HPV-6 (40) and DNA hybridization and restriction enzyme analyses have shown it to have 25% homology with laryngeal papilloma virus DNA, HPV-11 (41, 42). Hybridization studies using cloned HPV-6 genomic sequences have shown that 93 percent of all genital warts screened contained DNA sequences homologous to HPV-6 (41).

Condyloma acuminata has a preference for moist mucosal surfaces. These epithelial proliferations have a predilection for the genital area and are found frequently in sexually active males and females. The disease presents in females as verrucous lesions on the perineum, vaginal mucosa or portio-vaginalis of the cervix and in males on the genitalia, perianal or rectal mucosa. Each small exophytic keratinized vegetation arises separately from the skin or mucosa. The low power microscopic appearance suggests fronds of actively growing epithelium. Each frond is supported by a thin connective tissue branch which bears vessels leading to the epithelial layer. The condyloma is infiltrated with inflammatory cells throughout the subepithelial zone and epithelial cells occasionally exhibit atypical hyperplasia and dysplasia.

Early studies first reported nearly a decade ago demonstrated the utility of topical application of a vaseline-lanolin ointment containing crude human leukocyte interferon (43, 44). The results of this and other studies are outlined in the following table:

	Results Reported from Study of:			
	Ikic et al. (43)	Ikic et al. (44)	Wallach et al. (45)	Gall et al. (46)
Disease Severity:	Unknown	Unknown	Unknown	Resistant/ severe
Prior Therapy:	Unknown	Unknown	Unknown	Podophyllin
Interferon:	Leukocyte	Leukocyte	Fibroblast	WELLFERON®
Route:	Topical	Topical	i.m./s.c.	i.m.
Formulation:	Ointment	Ointment	Solution	Solution
Dose:	.04 Mu/gm	.04 Mu/gm	5 Mu	5 Mu/m ²
Schedule:	5-6 x daily	5-6 x daily	t.i.w.	daily x 28; then t.i.w.
Duration:	2-8 wks	2-8 wks	6 wks	6 wks
Complete Responses:	36/40	4/10	5/5	8/16
Partial Responses:	Unknown	6/10	0/5	7/16

Interpretation of results from the three earliest studies (43, 44, 45) is difficult because prior therapy, history, and extent of disease were not reported.

A 17 patient pilot study has examined the effects of systemic WELLFERON® on genital warts in women who have failed a minimum of 10 Podophyllin treatments (46). WELLFERON was administered at 5 Mu/m²/day intramuscularly for 28 days followed by three doses per week for 2 weeks. Sixteen patients completed therapy; one patient withdrew from the study after 1 week due to side effects of the interferon. Eight of 16 had complete regression (CR), 7 had good partial responses (PR) and one patient did not respond to treatment. All patients on this study required dose reductions to 3 Mu/m² due to decreased WBC's and/or side effects such as headaches, nausea and vomiting.

A Phase II study to examine the efficacy of 1 vs. 3 Mu/m² of WELLFERON given intramuscularly or subcutaneously to patients with resistant disease is being performed at four institutions. The study design requires daily injections for 14 days followed by treatment three times weekly for one month. Patients experiencing partial regression may continue for an additional month and nonresponding patients have doses escalated from 1 to 3 or 3 to 5 Mu/m². To date, the most experience has been gained at Duke Medical Center where 28 patients (24F/4M) have received the full six weeks of therapy. Responses are: 9 CR, 12 PR, 4 S and 2 NR. One patient withdrew from the study before completing an adequate course of treatment. Ten of 14 patients started at 1 Mu/m² have required dose escalations in order to achieve optimal responses. Only 4 patients treated at 3 Mu/m² have been escalated to 5 Mu/m² after 6 weeks of therapy.

Based on these significant responses with WELLFERON in Phase I and II studies, the present Phase III/IV trial is being undertaken to establish the effects of systemic administration of 3 Mu/m² of WELLFERON on the regression of severe recurrent genital warts. The antiviral effects of human lymphoblastoid interferon

will be measured in LAS patients with recurrent/resistant disease on a dose and schedule known to be effective; namely, 3 Mu/m²/day x 14 followed by 3 doses per week for an additional 4 weeks.

2.5 Acyclovir for Herpes Virus Infections

The rationale for the use of acyclovir (ZOVIRAX®) in treating herpes virus infections in LAS patients is based on its high selectivity for these viruses. Extensive clinical trials have demonstrated the safety and efficacy of topical administration of ZOVIRAX for recurrent herpes labialis and genitalis. In addition, studies with intravenous administration have proven its effectiveness in treating acute viral infections in both immunocompetent and immunocompromised patients. Multiple-dose studies have been performed to evaluate the efficacy, safety, pharmacokinetics and bioavailability of oral acyclovir as well.

Intravenous administration of ZOVIRAX Sterile Powder is efficacious for varicella and zoster infections in patients with competent and compromised immune status. A multicenter trial conducted in immunocompromised children with chickenpox infections resulted in 0/7 ZOVIRAX treated patients developing pneumonitis; whereas, 5/11 placebo recipients did. In a similar study, 94 patients with zoster infections (shingles) were evaluated. Fifty-two patients received acyclovir and 42 received placebo. ZOVIRAX therapy resulted in significant reductions in cutaneous dissemination, visceral dissemination, and the number of patients deemed treatment failures. Two controlled trials in immunocompetent patients with acute zoster infection or trigeminal zoster have corroborated these results. ZOVIRAX administered at a dose of 5 mg/kg every 8 hours for 5 days significantly shortened the time of new lesion formation, time to vesicle collapse, and time to complete crusting of lesions. Two additional randomized placebo-controlled trials at different doses of ZOVIRAX have shown that patients treated with acyclovir had a significantly abbreviated time of viral shedding when compared to placebo recipients.

ZOVIRAX® Capsules have been employed in controlled clinical trials in patients with initial and recurrent genital herpes. Proportional increases in bioavailability were observed through doses of 600 mg with higher than anticipated values at 800 mg doses. Oral administration of ZOVIRAX has shown significant decreases in healing time, severity and duration of pain, new lesion formation, and viral shedding when compared to placebo. In patients with initial episodes of genital herpes, inguinal adenopathy and headache resolved significantly faster in the ZOVIRAX treated group. Likewise, dysuria in females was resolved more quickly. Early treatments significantly improved time to crusting and complete healing in females and effectively reduced new lesion formation in both sexes. To date, data support that therapy should be initiated as early as possible following onset of signs and symptoms to maximize clinical benefit.

3.0 STUDY SUMMARY

This study will measure the efficacy of interferon in treating resistant/recurrent condyloma acuminata or acyclovir in treating primary or recurrent herpes virus infections in patients with LAS. Patients will be assigned to receive either ZOVIRAX (Regimen A) or WELLFERON® (Regimen B) according to their original disease diagnosis. The time course involved for regression of condyloma acuminata or healing of herpes lesions are critical portions of this study. Additionally, interferon-induced or acyclovir-associated side effects will be monitored at regular intervals during this trial. Disease responses will be recorded on schematic drawings and confirmed with photographs on an every two week schedule during the study. Patients assigned to WELLFERON will receive daily subcutaneous injections for 14 days then 3 x weekly for 4 weeks at a dose of 3 Mu/m² per injection. If a complete response (CR) has occurred within 6 weeks, the patients will be observed until recurrence. If a partial (PR) or no response (NR) has occurred after the first 6 weeks, the patient will be observed for 4 weeks. Patients who were PR after initial 6 weeks or experience recurrence during observation will receive a

second six-week course of ZOVIRAX® for herpes infection or WELLFERON® for condylomata. Patients who remain nonresponders (NR) after observation will receive combined therapy of acyclovir 400 mg tablets every 8 hours daily plus interferon 3 Mu/m² s.c. 3 x weekly for a total of 6 weeks. Any patient who develops disease, either herpes virus infection or condyloma acuminata, other than their original diagnosis may cross to the appropriate arm of study for that disease.

3.1 Patient Selection

Thirty homosexual male patients with the syndrome of prolonged unexplained lymphadenopathy and presenting with recurrent/resistant condyloma acuminata or herpes simplex infection will be entered on study. Patients will be under care in the AIDS clinic, UCLA Center for Health Sciences.

3.1.1 Eligibility Criteria

All patients must have:

- 1) Lymphadenopathy with pathologic, clinical appearance (1-3 cm diameter) and involving at least two regional chains above diaphragm
- 2) Lymphadenopathy for >6 months duration.
- 3) Biopsy proven follicular hyperplasia, and absence of involution and malignancy.
- 4) T-helper/T-suppressor ratio <0.8.
- 5) Diagnosis of condyloma acuminata or culture-proven herpes simplex or clinical herpes zoster.
- 6) Condylomata present for >3 months.
- 7) At least 2 previous podophyllin or equivalent treatments (cryo, laser, surgery) for condylomata.
- 8) Measurable condyloma or herpes lesions.
- 9) Signed informed consent.

3.1.2 Exlcusions

- 1) Less than 18 years old.
- 2) Patients with AIDS or oral candidiasis.
- 3) Malignant degeneration in excised tumor.

- 4) Immunological therapy within previous 3 months.
- 5) Renal insufficiency (serum creatinine >1.4).
- 6) Anemia (Hgb <10 gm/dl), leukopenia ($\leq 1500/\text{mm}^3$), thrombocytopenia ($<100,000/\text{mm}^3$), clinical or laboratory coagulopathy.
- 7) Impaired liver functions (SGOT >1.5 mg/dl).
- 8) Known hypersensitivity to Neomycin or Polymyxin B.
- 9) Significant cardiac, pulmonary, gastrointestinal, renal, or other conditions which may impair tolerance of acute pyrexial reactions or blood pressure changes associated with interferon administration.
- 10) Unavailability for 6 weeks treatment and 4 weeks observation.
- 11) Not accessible geographically for follow-up.
- 12) Patients receiving steroids, cytotoxic immunosuppressive agents or radiotherapy.

4.0 THERAPEUTIC AGENTS

4.1 WELLFERON® (Human Lymphoblastoid Interferon)

4.1.1 Product Description

WELLFERON is a purified preparation of human alpha interferons from cultured human lymphoblastoid cells. These cells are induced with Sendai virus which results in synthesis and secretion of interferons. WELLFERON is isolated, concentrated and purified from cell-free supernatants to $\geq 95\%$ purity. Human lymphoblastoid interferon has been purified to a level of 2×10^8 international units (IU) of human alpha interferon per mg protein.

Biological activity of WELLFERON is expressed in megaunits (Mu) where 10^6 IU equal 1 Mu. This unitage is determined in a viral cytopathic effect inhibition assay standardized against the international alpha interferon standard 69/19. Extensive experimental work has demonstrated that WELLFERON is nearly identical in

its chemical, physical, immunologic and biologic properties to interferon derived from buffy coat cells of human blood. It contains at least 12 human alpha interferon subtypes.

4.1.2 Formulation and Stability

WELLFERON® is formulated in tri-glycine buffered physiologic saline with human serum albumin added as stabilizer. Prior to blending, $\geq 95\%$ of the material is purified interferon protein. Because albumin accounts for 90% or more of the protein in the final product, the specific activity of the interferon becomes correspondingly reduced.

WELLFERON is supplied in 1.0 ml vials. Interferon content of final containers is determined by titration in an antiviral assay and expressed in mega units (Mu) per vial. WELLFERON vials are routinely filled at concentrations of approximately 3 or 10 Mu/vial; the precise unitage for each individual lot is specified on the carton label.

WELLFERON is supplied as a frozen solution. Storage must be at or below -20°C and WELLFERON must not be thawed and refrozen repeatedly. It may be stored frozen for up to 12 months. It contains no preservatives, antimicrobial or antifungal agents. Thawed WELLFERON may be stored in unentered vials at $4-8^{\circ}\text{C}$ for up to 6 months. Vials entered under pharmaceutically sterile conditions (laminar flow hoods) may be stored at $4-8^{\circ}\text{C}$ for up to 48 hours and may be re-entered.

4.1.3 Administration and Supply

WELLFERON will be injected subcutaneously on the anterior portion of the thigh in rotation of sites at a dose of 3 Mu/m^2 daily for 14 days and 3 x weekly for 4 weeks thereafter.

WELLFERON will be supplied in sequentially numbered vials. Records of drug used and carton labels will be

retained in a CTM Inventory folder supplied by B.W. Co. Vials should not be shaken or inverted as loss of drug may occur due to liquid being trapped in the small neck of the vial. All empty vials, vials with remaining drug, unused vials and CTM Inventory folder will be returned to Burroughs Wellcome Co. for accountability.

4.1.4 Pharmacology of WELLFERON®

WELLFERON has been studied in a series of Phase I trials employing doses from 0.1 to 50 Mu/m² administered by i.m. or i.v. routes. Doses as high as 200 Mu/m² have been given by continuous 24-hour infusions. Serum interferon pharmacokinetics have been studied systematically within the limits inherent in bioassays and differences in individual subjects.

In a Phase I study in which 40 patients received 0.1-50 Mu, serum interferon levels were detectable at doses of 5 Mu or greater by either route (47). The peak levels were dose related with i.v. peaks higher than their i.m. counterparts (compare Figs. 1 & 2 below).

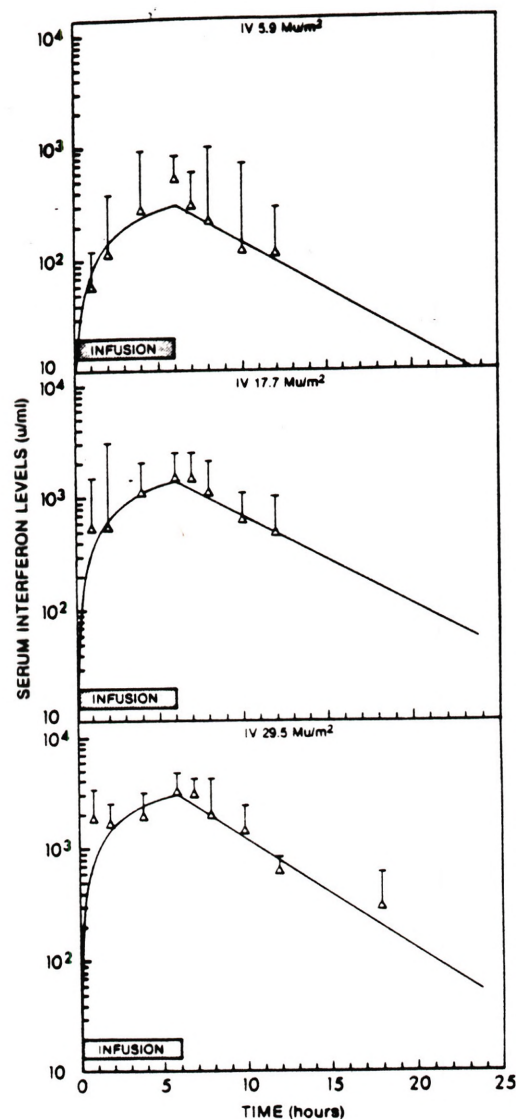


Fig. 1. Analyses of serum interferon levels following 6 hr intravenous infusions of WELLFERON® at 3 different doses (47). Interferon was administered in total doses of 10, 30 or 50 Mu which correspond to approximately 6, 12 and 30 Mu/m², respectively. These curves represent the best fit as determined by a single compartmental pharmacokinetics model. Each point represents the mean of 13-20 individual values and the bars are S.E.M.

Peak levels following i.m. administration occur 6-7 hours after injection (Fig. 2) and this is consistent with earlier data reported for lower doses of WELLFERON. Following termination of intravenous infusions there is a rapid decline in serum interferon levels (Fig. 1). Analyses of the data plotted in Figures 1 and 2 indicate that areas under the curve are approximately 25% greater following i.m. injections at doses of 10 and 30 Mu. In another study in which daily 24-hour infusions were given, a plateau, which was dose related through 30 Mu/m², was achieved (48). Infusions of 50-200 Mu/m² did not result in higher serum levels.

A comparison of data from several WELLFERON® studies supports several general conclusions:

- a. serum levels are dose related and the kinetics in serum show an initial fall-off with $T_{1/2}$ of 10-12 hrs following i.m. dosing.
- b. "accumulation" can occur as reflected by trough levels at 24 hours; this is dependent on the dose level and frequency of administration.
- c. individual patients develop somewhat variable levels of serum interferon activity with some patients consistently higher than others.

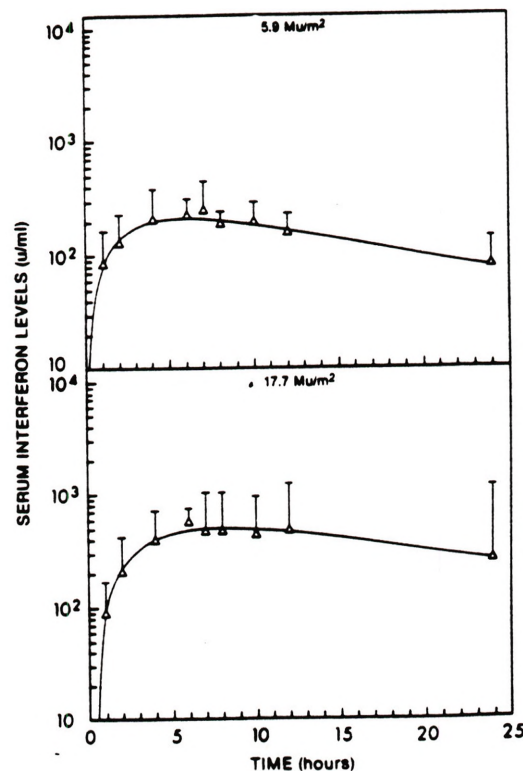


Fig. 2. Analyses of serum interferon levels following intramuscular injection of WELLFERON at 2 doses (47). The data are presented as described in the legend to Figure 1. Each point represents the average of 10 values.

The results described above for pharmacokinetic studies with WELLFERON demonstrate that the clearance rates and serum half-lives for this mixture of alpha interferons are similar to those reported for other interferons. Studies conducted with leukocyte-derived (49) or bacteria-derived (50) alpha interferons report similar findings at comparable doses.

4.1.5 Side Effects and Toxicity of WELLFERON®

The symptomatic side effects and toxicities related to WELLFERON administration are similar to those ascribed to both native leukocyte and recombinant DNA-derived interferons. Lists of these are recorded respectively in Tables I and II below.

TABLE I
WELLFERON SIDE EFFECTS

<u>Endotoxin Reaction</u>	<u>Flu Syndrome</u>
Fever +/- Chill	Anorexia
Tachycardia	Myalgia
Headache	Malaise, Fatigue
	Weight Loss
<u>Gastrointestinal</u>	<u>Neurologic</u>
Nausea +/- Emesis	Paresthesias
Diarrhea	Somnolence
Dysgeusia	Confusion
	Seizures (rare)
<u>Others</u>	
Alopecia	
Induration at Injection Site (rare)	

The most commonly occurring side effect of WELLFERON has been a febrile response. Intramuscular injections of WELLFERON at doses from 0.3 up to 30 Mu/m² resulted in temperature rises between 1 and 8 hours post-injection (47). These pyrexial responses subsided with subsequent injections and were ameliorated with salicylates. Malaise and fatigue have been the most common complaints from patients even at the lowest doses given. Nausea and vomiting have been controlled with antiemetics. Anorexia accompanied by weight loss has been a problem in two instances but both were juvenile patients who recovered after interferon was stopped. Several adult patients with hepatitis B virus infections and two pediatric

patients with laryngeal papillomatosis have reported significant hair loss during WELLFERON® treatment. Reports of local induration or irritation at the sites of injection have been rare.

TABLE II
WELLFERON TOXICITIES

<u>Hematologic</u>	<u>Neurologic</u>
Leucopenia	Weakness
Granulocytopenia	EEG Slowing
Thrombocytopenia	Delta Bursts
Coagulopathy (rare)	
<u>Gastrointestinal/Chemical</u>	<u>Cardiovascular</u>
Hepatic Enzyme ↑↑	Hypertension
BUN ↑ (rare)	Hypotension
Ca ↓ (rare, high dose)	

WELLFERON has been administered by intravenous infusions at doses escalating from 5 to 200 $\text{Mu}/\text{m}^2/\text{day}$ in Phase I studies (47, 48). Continuous i.v. infusion was adopted after initial attempts at bolus delivery produced some severe hypotensive episodes. Similar patterns of side effects and clinical toxicities were observed with severe neurological toxicities noted at doses of 150 and 200 $\text{Mu}/\text{m}^2/\text{day}$ (48). Other neurological abnormalities included paresthesias and mental state modifications such as lack of concentration and confusion. Documentation of CNS side effects has shown that continuous i.v. infusion of 100 $\text{Mu}/\text{m}^2/\text{day}$ for 7 days caused reversible EEG changes in all patients examined (51). These alterations were measured even when there was no clinical evidence of CNS disturbances. Transient changes in hepatic functions were observed in all patients with marked increases in alkaline phosphatase and transaminase levels (51). Nine pediatric patients with acute nonlymphocytic leukemia have been treated by continuous infusions

with 15, 20 or 30 Mu/m²/day of WELLFERON® for 10 days. All but one of these individuals developed coagulation abnormalities between days 4 and 8 of their infusion cycles. Measurement of coagulation parameters demonstrated elevations in PT and PTT values. One patient with advanced ovarian cancer experienced severe renal and hepatic dysfunction following high dose (20 Mu/m²/day) continuous infusion of WELLFERON. Seven patients with advanced renal cell carcinoma have exhibited severe rises in SGOT levels or granulocytopenia requiring dose reductions or discontinuation of i.m. injections of 30 Mu/m²/day.

The experience with WELLFERON to date indicates that most severe toxicities associated with human lymphoblastoid interferon treatment occur at relatively high doses (>10 Mu/m²). Many of these serious reactions appear to be related to the patient's underlying disease, previous therapy, age and performance status at the time of entering the interferon study. Several incidents in patients receiving low dose therapy of 5 Mu/m² require close attention to patients with neuroendocrine disorders as they may be relatively more sensitive to interferon's effects. In addition, chronic dosing with WELLFERON will require monitoring of white blood cell counts and observation for any long-term side effects on hepatic functions.

4.2 ZOVIRAX® (Acyclovir)

4.2.1 Product Description and Mechanism of Action

ZOVIRAX is an antiviral drug with potent activity against herpes viruses. It is a synthetic acyclic purine nucleoside analog with in vitro activity against herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella-zoster, Epstein-Barr and cytomegalovirus. Acyclovir is a white, crystalline powder with a molecular weight of 225 Daltons and a maximum solubility in water of 1.3 mg/ml.

The inhibiting activity of acyclovir is highly selective. Herpes simplex virus-coded thymidine kinase converts acyclovir into acyclovir monophosphate. Cellular thymidine kinase does not effectively use it as a substrate. The monophosphate form is further converted to diphosphate and triphosphate by a number of cellular enzymes. The acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication.

4.2.2 Formulation and Stability

ZOVIRAX® Tablets conform to Burroughs Wellcome Pharmaceutical and Research Lab. CTM number _____. Each tablet contains 800 mg or 400 mg acyclovir with inert filler (lactose, magnesium stearate, sodium lauryl sulfate and corn starch). Tablets should be stored at room temperature in well-closed containers and should be dispensed in light-resistant bottles.

4.2.3 Administration

ZOVIRAX should be administered as one 800 mg tablet five times daily, every 4 hours, for 14 days; then, one 400 mg tablet three times daily, every 8 hours, for an additional 4 weeks. This treatment cycle may be repeated as described in Section 3.0.

4.2.4 Pharmacology

Acyclovir has been administered orally to both immunocompromised and immunocompetent patients in dose ranging studies. A summary of the pharmacokinetic data from these studies are outlined below:

<u>Dose</u>	Mean Peak Plasma Conc. at Steady State <u>µg/ml</u>	Mean Trough Plasma Conc. at Steady State <u>µg/ml</u>	AUC (Area under con- centration/ time curve)
Immunocompromised Patients			
200 mg q 4 hrs, 5 days	0.5	0.3	7.9
400 mg q 4 hrs, 5 days	1.2	0.6	16.7
600 mg q 4 hrs, 5 days	1.3	0.8	21.0
800 mg q 4 hrs, 5 days	2.7	1.8	63.8
Immunocompetent Patients			
400 mg q 4 hrs, 5 x day, 5 days	1.0	0.6	13.3
600 mg q 4 hrs, 5 x day, 5 days	1.5	0.7	19.1
800 mg q 6 hrs, 5 days	1.5	0.7	26.0

4.2.5 Side Effects and Toxicities

No significant side effects, other than occasional single episodes of nausea or diarrhea, have been observed in patients studied to date. Controlled clinical trials also have not produced evidence of acute toxicity resulting from oral administration of acyclovir.

The most frequent adverse reaction reported during controlled studies of ZOVIRAX® Capsules have been nausea and/or vomiting in 5 of 306 patients (1.7%) and headache in 3 of 306 (1%). In patients receiving placebo, 2 of 290 (0.7%) experienced nausea/vomiting, and 1 of 290 (0.4%) reported headaches. In all studies, there was no significant difference between the drug and placebo groups in the rate or type of reported adverse reactions. Additional adverse reactions have been reported in uncontrolled trials and have included nausea, headache, diarrhea and loose stools.

5.0 TREATMENT REGIMEN

5.1 Patient Entry/Assignment

Eligible LAS patients with resistant/recurrent condyloma acuminata or herpes simplex lesions will have entry and eligibility forms completed. Patients will then be to receive ZOVIRAX® (Regimen A) or WELLFERON® (Regimen B). Assignments will be made on the basis of the original disease diagnosis. All patients must meet the entry criteria for the syndrome of unexplained generalized lymphadenopathy.

5.2 Regimen A - ZOVIRAX for Herpes Simplex

Patients assigned to this arm of the study will receive ZOVIRAX orally as 800 mg or 400 mg tablets. ZOVIRAX will be administered as one 800 mg tablet q. 4 hrs. daily for 14 days followed by one 400 mg tablet q. 8 hrs. daily for 4 weeks.

Following six weeks of treatment, all patients will be observed for 4 weeks to document regression or recurrence of herpes simplex lesions.

5.3 Regimen B - WELLFERON for Condyloma Acuminata

Patients assigned to this arm of the study will receive WELLFERON by s.c. injections at a dose of 3 Mu/m² daily for 14 days followed by the same dose given 3 times per week for 4 weeks. Subcutaneous administration will be achieved by rotation of sites on the anterior aspect of the thigh in a volume of 0.5-1.0 ml per site. Following this 6 week period, all patients will be observed for 4 weeks to document regression or recurrence of disease.

5.4 Assessment of Response/Toxicities

Lesion measurements are to be recorded every two weeks and documented by photographs at the same intervals.

Condyloma lesions will be assessed by objective bidimensional measurements of anatomically localized warts and response will be graded by the criteria outlined in Section 8.0. Tissue biopsies should be obtained at entry for viral DNA subtyping. Repeat biopsies should be performed at week 7 and at the end of study in those patients with remaining wart tissue.

Side effects and toxicities related to interferon are to be assessed weekly during the first month of study and for the remainder of the study.

Herpes simplex lesions will be assessed by objective measurements of anatomically localized lesions. Responses will be graded by the criteria outlined in Section 8.0. Virus isolates will be obtained for characterization of HSV at entry. Repeat isolates, if available, should be obtained at week 7 and the end of study.

5.5 Additional Treatment of Disease

5.5.1 Second Course of Therapy

All patients experiencing a partial response during the initial 6 week treatment period and/or recurrence of disease while undergoing observation for 4 weeks are eligible to receive a second 6 week course of WELLFERON® or ZOVIRAX® as appropriate for their disease.

Any patient experiencing a complete regression and then recurrence of disease while off therapy is eligible for the second 6 week course of WELLFERON or ZOVIRAX.

5.5.2 Combined Interferon and Acyclovir Therapy

All patients experiencing no response (NR) to ZOVIRAX for Herpes simplex infections or to WELLFERON for Condyloma acuminata during the initial 6 week treatment and observation periods will be eligible for combined therapy. Nonresponders will receive ZOVIRAX as one 400 mg tablet q. 8 hours daily for six weeks concomitant with WELLFERON s.c. at 3 Mu/m²/injection 3 x weekly for 6 weeks.

5.5.3 Crossover to Other Treatment Arm

Any patient developing disease (either HSV infection or condyloma acuminata) other than their original diagnosis at any time during the course of study may crossover to the treatment arm appropriate for that disease.

5.6 Removal from Study

5.6.1 Toxicities - Patients developing unmanageable or life-threatening toxicities may be removed from the study at

the discretion of the physician, but Burroughs Wellcome Co. must be notified immediately (Dr. John K. Whisnant or Dr. Phillip K. Weck (919) 248-4160 or 248-4568, respectively). If after business hours, call the respective home numbers ((919) 942-3936 or 781-5771).

5.6.2 Patient refusal of further treatment; reasons must be noted on Data Collection Form.

5.6.3 Patients whose disease is progressing unacceptably will be removed in consultation with the Burroughs Wellcome monitor.

6.0 OBSERVATIONS/STUDIES TO BE RECORDED

6.1 Study Schedule

Laboratory studies, disease evaluations and other procedures/ observations are to be performed as outlined in the Activities Chart (see next page).

6.2 Prestudy Evaluations

Studies at entry should be performed within one week prior to initiation of interferon or acyclovir therapy.

6.3 Intervals for Disease Evaluations

Patients receiving WELLFERON® or ZOVIRAX® will be evaluated clinically with diagrams and photographs every two weeks. The patients' lesions will be mapped on a schematic drawing of the genital, perianal or rectal area and objective measurement will be by visual determination of the size and severity of lesions. Photographs will be used to confirm objective measurement.

6.4 Patient Performance/Side Effects

Karnofsky performance status should be determined prestudy and every other week thereafter. Drug-related side effects and disease symptoms should be evaluated at least biweekly. These side effects and symptoms will be recorded in a personal daily diary maintained by each patient.

6.5 Laboratory Data

Patients presenting with documented Condyloma acuminata or Herpes simplex will be evaluated by the following:

- 6.5.1 Hematology: Hemoglobin or hematocrit, WBC with differential, and platelet count at Entry, weeks 2, 3, and every two weeks.
- 6.5.2 Chemistry: SGOT, bilirubin, BUN, and creatinine at Entry, weeks 2, 3, and every two weeks.
- 6.5.3 Serum: For anti-interferon antibody studies, acid-labile interferon, and baseline interferon titers, 3.0 ml of serum will be obtained. Samples should be obtained at entry, day 1 hour 4, week 7 and end of study. The serum will be divided into 3 aliquots in 1.0 ml volumes and stored with proper identification at -20°C.
- 6.5.4 Tissue Specimens: Tissue for diagnosis of Condyloma acuminata must be obtained if not performed within last 6 months. If available, additional tissue will be obtained for DNA hybridization studies. All specimens will be snap-frozen in liquid nitrogen and stored at -80°C (see Appendix III).
- 6.5.5 Immunologic Studies: Blood will be drawn for quantitative immunoglobulin levels (IgG, IgA, and IgM) at entry, and end of study. Blood will be taken for determination of percentage and absolute numbers of T-helper and T-suppressor lymphocytes at entry, weeks 3, 7 and 11.
- 6.5.6 Virologic Studies: Specimens of urine, semen, and buffy coat cells obtained at entry, weeks 3, 7 and 11 will be cultured for CMV.
- 6.5.7 Lymph Node Biopsy: A finding of follicular hyperplasia in a node biopsy will be required prior to patient enrollment.

7.0 TREATMENT MODIFICATIONS/TOXICITY MANAGEMENT

7.1 General Principles

7.1.1 Supportive Management

Every effort will be made to manage constitutional symptoms and gastrointestinal toxicities with supportive care and appropriate therapeutics (e.g., antiemetics). If symptoms persist despite such efforts, dose modifications may be made as outlined below (Section 7.4). If dose modification is required for an abnormal laboratory finding, that test will be repeated in 72 hours.

An acute febrile response and related symptomatology commonly occurs following interferon exposure. It has been most pronounced with initial treatment and ameliorates with subsequent dosing. These physiologic and subjective disturbances are to be monitored on all patients throughout the entire trial period. Dose reductions may be made for such physiologic and symptomatic side effects when the grade is intolerable for a particular patient, considering the amelioration with daily dosing and symptomatic control with medication (see grading below).

7.1.2 Intervals for Dose Alterations

During the primary treatment period, dose modification for interferon-induced symptomatic toxicities will be made after that week's laboratory results are reviewed and will be based on the highest grade of toxicity observed during the previous week.

7.2 Severe or Life-Threatening Toxicities

Major toxicities may require patient withdrawal after consultation with the Study Monitor who must be notified of such occurrences immediately (see Section 5.6).

7.2.1 Hypotension and hypertension may occur on the first or subsequent dose of WELLFERON®. Clinically significant hypotension has been reported. Any rise or fall >20 mm Hg will be dealt with cautiously and proper supportive or pharmacologic management will be considered if changes in blood pressure persist or recur.

- 7.2.2 CNS toxicity, including grand mal seizure, has been reported, particularly in association with very high doses ($>100 \text{ Mu/m}^2/\text{day}$). Anticonvulsants may be used for control during continued interferon treatment. Lesser CNS toxicities include confusion, depression, diminished alertness and ability to concentrate normally.
- 7.2.3 Anaphylactic reaction. This has not been previously seen with WELLFERON®. If severe hypersensitivity (urticaria, bronchospasm) to interferon is seen, Study Monitor should be notified immediately.

7.3 Toxicity Grading for Dose Reductions

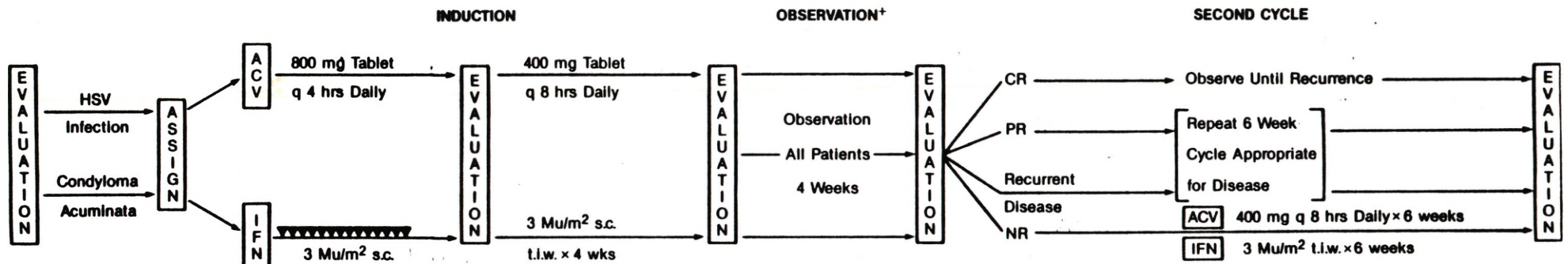
<u>Toxicity</u>	<u>Toxicity Grading</u>			
	(Mild) <u>Grade 1</u>	(Moderate) <u>Grade 2</u>	(Severe) <u>Grade 3</u>	(Life-threatening) <u>Grade 4</u>
Fever*	1°C over pretreatment to 38.6°C	38.7°C-39.7°C	>39.7°C	
Chills*	mild to moderate shaking	severe shaking	rigors	
Fatigue*	100% P.S.-feeling fatigue	50-100 P.S. significant fatigue	<50% P.S., depression extreme discomfort lethargy	
Malaise*	[Flu-like syndrome (myalgia, arthralgia)]			
	<6 hrs duration	6-24 hrs duration	>24 hours duration	
Nausea/* vomiting	Nausea only	Emesis <6 no antiemetics	Emesis >6 with antiemetics	
Headache*	<2 hrs not requiring analgesic	>2 hrs, but less than 24 or requiring analgesic	>24 hrs with or without analgesic	
Granulocytes	1000-1500	500-999	<500	Grade 3 plus infection
Platelets	<100,000	50-75,000	25-49,999	Grade 3 plus bleeding
SGOT	<2 x normal or patient's baseline	<3 x normal or patient's baseline	>3 x normal or patient's baseline	
Creatinine	1.5-1.9	2.0-2.5	>2.5	

*Dose reductions may be made at the discretion of the investigator.

**WELLFERON® FOR CONDYLOMA ACUMINATA
ZOVIRAX® FOR HERPES SIMPLEX
IN PATIENTS WITH UNEXPLAINED LYMPHOADENOPATHY SYNDROME**

PRIMARY OR RECURRENT HSV
SEVERE/RESISTANT CONDYLOMATA
(30)

UCLA MEDICAL CENTER
BURROUGHS WELLCOME CO.



WEEK:	Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
EVALUATIONS	*			*		*		*		*		*		*		*		*
HEMATOLOGY	*		*	*		0		*		0		*		*		0		*
CHEMISTRIES	*		*	*		0		*		0		*		*		0		*
BIOPSIES/ ISOLATES	*							*										*

+:Patients developing disease other than original diagnoses may cross to other arm.
0:Optional-to be repeated if previous laboratory values abnormal.

7.4 Dose Reductions (% of Starting Dose) by Toxicity Based on Highest Grade

<u>WELLFERON®</u>			
<u>100%</u>	<u>67%</u>	<u>33%</u>	<u>0</u>
1	2	3	4
	(1)	(2)	(3)

Number in parentheses indicates dose adjustments to be made only after a grade 2 or 3 toxicity occurs on two consecutive weeks at a given dose.

8.0 DISEASE ASSESSMENT

8.1 Disease Measurement

Condyloma acuminata or Herpes simplex lesions used for response determination must be bidimensionally measurable. Disease response will be followed by individual serial measurements performed every two weeks.

8.2 Definition of Response

8.2.1 Responders

Complete Response (CR) - complete disappearance of all objective evidence of disease; suspicious lesions will be biopsied.

Partial Response (PR) - decrease of 50% or more in sum of products of diameters of measurable lesions.

Minimal Partial Response (MPR) - decrease of 25-50% of sum of products of diameters of measurable disease.

Stable Disease (SD) - decrease of <25% or increase of <25% in sum of products of diameters of measurable disease.

8.2.2 Nonresponders (progression) - increase of $\geq 25\%$ in sum of products of diameter of measurable lesions.

9.0 STATISTICAL CONSIDERATIONS

9.1 Experimental Design

This is a Phase III/IV study designed to test the therapeutic effectiveness of interferon alone in severe/resistant Condyloma acuminata or acyclovir alone in herpes virus infections in LAS patients. It will test combination therapy in patients who do not respond to acyclovir treatment for herpes virus infections. Patients will be assigned to treatment with acyclovir or interferon based on their original diagnosis. Patients will be excluded from efficacy analysis if they receive less than the 6 weeks of primary therapy due to toxicities or withdrawal from study.

9.2 Sample Size

Thirty patients with diagnosed unexplained lymphadenopathy syndrome (LAS) will be entered on this study. Every effort will be made to assign 15 patients to each arm of the study to evaluate the effectiveness of either acyclovir or interferon in the treatment of viral infections in patients with this syndrome.

10.0 STUDY MANAGEMENT AND REPORTING PROCEDURES

10.1 Patient Consent and IRB Approval

The investigator is responsible for patient care and consent by the patient or family. Written informed consent must be obtained prior to entry of any patient.

No patients are to be entered on this protocol until after the institution's Human Investigation Committee has approved it. A copy of this institutional approval will be provided to Burroughs Wellcome Co. before drug is provided.

10.2 Drug Acquisition and Inventory Control

10.2.1 WELLFERON®

Sufficient WELLFERON for the primary treatment course for two patients will be provided from Burroughs Wellcome Co. to each institution at the time of FDA registration. When the investigator's office notifies

the Company of patient entry, additional interferon will be sent to the study institution. Any requests for interferon should be directed through the Burroughs Wellcome study monitor.

A record for all WELLFERON® used in this study must be maintained by the Dispensing Pharmacy. A tear-off label will be attached to each WELLFERON carton, and it will be placed on the Clinical Trial Material Inventory Control Form for accounting of vials for individual patients. ALL unused drug and empty drug vials must be returned to a Burroughs Wellcome staff member.

10.2.2 ZOVIRAX®

ZOVIRAX supplies for the primary treatment of two patients will be made available from Burroughs Wellcome at time of registration with FDA. Additional tablets should be requested through the study monitor. All unused drug will be returned to Burroughs Wellcome Co. after completion of study.

10.3 Patient Records

10.3.1 Hospital Records

Hospital records for patients on this study are the responsibility of the investigator.

10.3.2 B.W. Data Collection Form

The Sponsor (Burroughs Wellcome Co.) will supply a booklet of information (Information for Investigators), a final protocol, and an individual data collection form (DCF) for each patient. These are the property of the Sponsor and are considered confidential. The completed original DCF will be collected by a Burroughs Wellcome staff member and a copy will be provided to the investigator.

10.4 Publications

The study of these patients, data on the use of WELLFERON and results of all laboratory studies are considered private

and confidential. The progress and results of this study will not be presented or published without agreement between the investigator and Wellcome Medical Staff at Research Triangle Park, NC. All abstracts and publications will be reviewed by the Wellcome Medical Staff prior to submission for publication or presentation.

11.0 REFERENCES

1. Update on acquired immune deficiency syndrome (AIDS)-United States. Morbid. Mortal. Weekly Rep. 31:507, 1982.
2. Gottlieb, M.S. Schroff, R. Schanker, H.M., et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired immunodeficiency. N. Engl. J. Med. 305:1425, 1981.
- (5) 3. Schroff, R.W., Gottlieb, M.S., Prince, H.E., et al. Immunologic studies of homosexual men with immunodeficiency and Kaposi's sarcoma. Clin. Immunol. Immunopath. 27:300, 1983.
4. Update: acquired immunodeficiency syndrome (AIDS)-United States. Morbid. Mortal. Weekly Rep. 32:688, 1984.
- (3) 5. Persistent, generalized lymphadenopathy among homosexual males. Morbid. Mortal. Weekly Rep. 31:249, 1982.
- (4) 6. Fernandez, R., Mouradian, J., Metroica, C. and Davis, J. The prognostic value of histopathology in persistent generalized lymphadenopathy in homosexual men. N. Engl. J. Med. 309:185, 1983.
- Midway (6) 7. DeStefano, E., Friedman, R.M., Friedman-Kien, A.E., et al. Acid-labile human leukocyte interferon in homosexual men with Kaposi's sarcoma and lymphadenopathy. J. Inf. Dis. 146:451, 1982.
8. Gold, J.W.M., Sears, C.L., Henry, S. et al. Lymphadenopathy in homosexual men and development of the acquired immune deficiency syndrome. Clin. Res. 31:363A, 1983.
9. Volberding, P. Therapeutic approaches in Kaposi's sarcoma. In, Proc. UCLA Symp. on AIDS. J. Cell. Biochem., 1984 (in press).

10. Isaacs, A. and Lindemann, J. Virus interference. I. The interferon. Proc. Roy. Soc. B147:268, 1957.
11. Weck, P.K., Apperson, S., May, L. and Stebbing, N. Comparison of the antiviral activities of various cloned human interferon-alpha subtypes in mammalian cell cultures. J. Gen. Virol. 57:233, 1981.
12. Stewart, II, W.E. The Interferon System. Springer, Wien, New York, 1981.
13. Came, P.E. and Carter, W.E. Interferon and Their Applications. Springer-Verlag, New York, Handb. Exp. Pharm. 71, 1984.
14. Baron, S., Dianzani, F. and Stanton, G.J. The Interferon System: A Review to 1982-Parts I and II. Tex. Rep. Biol. Med. 41, 1982.
15. Friedman, R.M., Baron, S., Buckler, C.E. and Steinmuller, R.I. The role of antibody, delayed hypersensitivity, and interferon production in recovery of guinea pigs from primary infection with vaccinia virus. J. Exp. Med. 116:347, 1962.
16. Gresser, I., Tovey, M.G., Bandu, M.T., Maury, C. and Brouty-Boye, D. Role of interferon in pathogenesis of virus disease in mice as demonstrated by the use of anti-interferon serum. I. Rapid evaluation of EMC virus infection. J. Exp. Med. 144:1305, 1976.
17. Haglund, S., Lundquist, P.G., Cantell, K. and Strander, H. Interferon therapy in juvenile laryngeal papillomatosis. Arch. Otolaryngol. 107:327, 1981.
18. Goepfert, H., Sessions, R.B., Gutterman, J.U., et al. Leukocyte interferon in patients with juvenile laryngeal papillomatosis. Ann. Otol. Rhinol. Laryngol. 91:431, 1982.
19. McCabe, B.F. and Clark, K. Interferon and laryngeal papillomatosis: the Iowa experience. Ann. Otol. Rhinol. Laryngol. 92: 2, 1983.
20. Bomholt, A. Interferon therapy for laryngeal papillomatosis in adults. Arch Otolaryng. 109: 550, 1983.

21. Weimar, W., Tenkate, F.J.P., Masurel, N., et al. Double-blind study of leukocyte interferon administration in chronic HB_sAg-positive hepatitis. *Lancet* 1: 336, 1980.
22. Scullard, G.H., Pollard, R.B., Smith, J.L., et al. Antiviral treatment of chronic hepatitis B virus infection: changes in viral markers with interferon combined with adenine arabinoside. *J. Infect. Dis.* 143: 772, 1981.
23. Scullard, G.H., Andres, L.L., Greenberg, H.B., et al. Antiviral treatment of chronic hepatitis B virus infection: improvement in liver disease with interferon and adenine arabinoside. *Hepatology* 1: 228, 1981.
24. Merigan, T.C., Rand, K.H., Pollard, R.B., et al. Human leukocyte interferon for treatment of herpes zoster in patients with cancer. *New Engl. J. Med.* 298: 981, 1978.
25. Merigan, T.C., Gallagher, J.G., Pollard, R.B. and Arvin, A.M. Short course human leukocyte interferon in treatment of herpes zoster in patients with cancer. *Antimicrob. Agents Chemother.* 19: 193, 1981.
26. Arvin, A.M., Kushner, J.H., Feldman, S. and Merigan, T.C. Human leukocyte interferon for the treatment of varicella in patients with malignancy. *New Engl. J. Med.* 306: 761, 1982.
27. Pazin, G.J., Armstrong, J.A., Lam, M.T., et al. Prevention of reactivated herpes simplex infection by human leukocyte interferon after operation on the trigeminal root. *New Engl. J. Med.* 301: 225, 1979.
28. Jones, B.R., Coster, D.J., Falcon, M.G. and Cantell, K. Topical therapy for ulcerative herpetic keratitis with human interferon. *Lancet* 2: 128, 1978.
29. Sundmacher, R., Cantell, K. and Neumann-Haefelin, D. Combination therapy of dendritic keratitis with trifluorothymidine and interferon. *Lancet* 2: 687, 1978.
30. Meyers, J.D., McGuffin, R.W., Bryson, Y.J., et al. Treatment of cytomegalovirus pneumonia after marrow transplant with combined vidarabine and human leukocyte interferon. *J. Infect. Dis.* 146: 80, 1982.

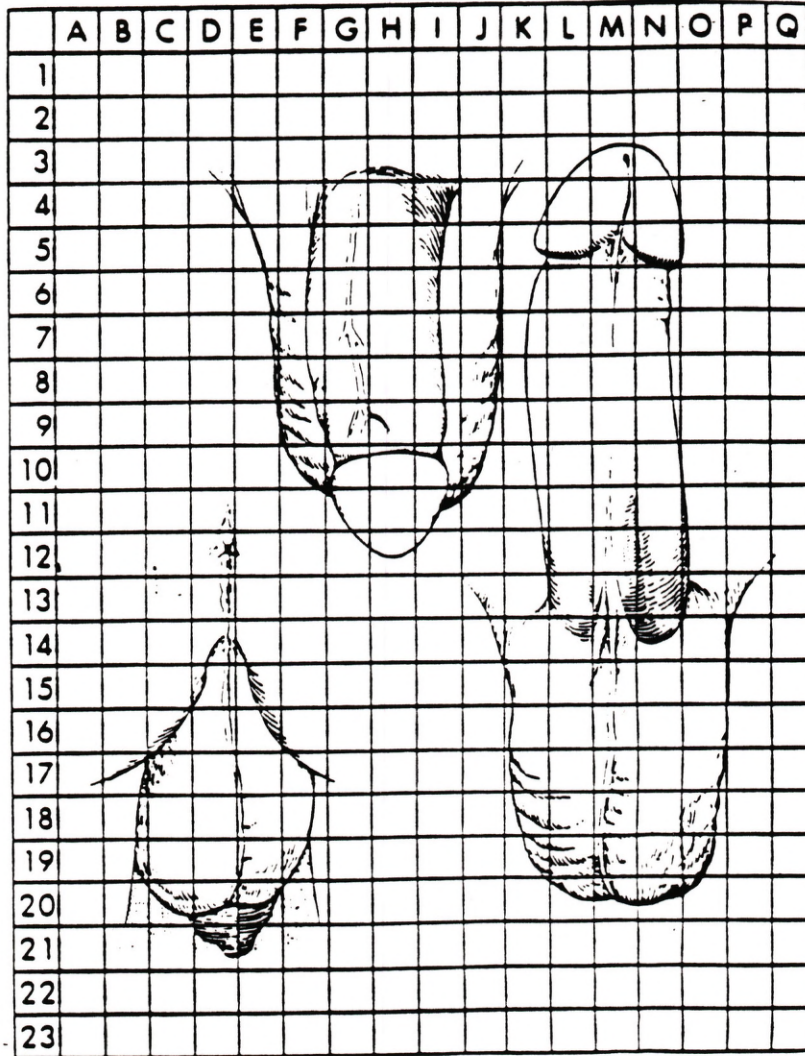
31. Hirsch, M.S., Schooley, R.T., Cosimi, A.B., et al. Effects of interferon-alpha on cytomegalovirus reactivation syndromes in renal-transplant recipients. *New Engl. J. Med.* 308: 1489, 1983.
32. Elion, G.B. Mechanism of action and selectivity of acyclovir. *Am. J. Med.* 73(1A):7, 1982.
33. King, D.H. and Galasso, G. Proceedings of a symposium on acyclovir. *Am. J. Med.* vol. 73, 1982.
34. Bryson, Y.V., Lovett, M., Taylor, S. et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. *N. Engl. J. Med.* 308:916, 1983.
35. Reichman, R.C., Badger, G.J., Mertz, G.J. et al. Orally administered acyclovir in therapy of recurrent herpes simplex genitalis: a controlled trial. *J. Am. Med. Assoc.* (in press).
36. Oriel, J.D. and Almeida, J.D. Demonstration of virus particles in human genital warts. *Br. J. Venereal Dis.* 46:37, 1970.
37. Dunn, A.E.G. and Ogilvie, M.M. Intranuclear virus particles in human genital wart tissue: observation on the ultrastructure of the epidermal layer. *J. Ultrastructure Res.* 22:282, 1968.
38. Gissman, L., Pfister, H. and Zur Hausen, H. Human papilloma viruses (HPV): characterization of four different isolates. *Virology* 76:569, 1977.
39. Zur Hausen, H. and Gissmann, L. Papillomaviruses. *In: Viral Oncology*, G. Klein (ed.), p. 433, Raven Press, New York, 1980.
40. Gissmann, L. and Zur Hausen, H. Partial characterization of viral DNA from human genital warts (condylomata acuminata). *Int. J. Cancer* 25:605, 1980.
41. Gissmann, L., De Villiers, E.M. and Zur Hausen, H. Analysis of human genital warts (condylomata acuminata) and other genital tumors for human papilloma virus type 6 DNA. *Int. J. Cancer* 29:143, 1982.
42. Gissmann, L., Diehl, V., Schultz-Conlon, H.J., and Zur Hausen, H. Molecular cloning and characterization of human papilloma virus DNA derived from a laryngeal papilloma. *J. Virol.* 44:393, 1982.

43. Ikic, D., Orescanin, J., Krusic, Z., et al. Preliminary study of the effect of human leukocyte interferon on condylomata acuminata in women. Proc. Symp. Clinical Use of Interferon, p. 223, Zagreb, 1975.
44. Ikic, D., Bosnic, N., Smerdel, S., et al. Double-blind clinical study with human leukocyte interferon in the therapy of condylomata acuminata. Proc. Symp. Clinical Use of Interferon, p. 229, Zagreb, 1975.
45. Wallach, D., Shattner, A., Merlin, G., et al. Interferon-induced proteins: biological functions and clinical applications. In: Interferons, p. 449, Academic Press, New York, 1982.
46. Gall, S.A., Hughes, C.E., Weck, P. and Whisnant, J. Interferon for the treatment of resistant condyloma acuminata. Gynecol. Oncol., 1984 (in press).
47. Knost, J.A., Sherwin, S.A., Abrams, P.G., et al. The treatment of cancer patients with human lymphoblastoid interferon: a comparison of two routes of administration. Cancer Immunol. Immunother. 15: 144, 1983.
48. Rohatiner, A.Z.S., Balkwill, F.R., Griffin, D.B., et al. A Phase I study of human lymphoblastoid interferon administered by continuous intravenous infusion. Cancer Chemother. Pharmacol. 9: 97, 1982.
49. Emodi, G., Just, M., Hernandez, R. and Hirt, H.R. Circulating interferon in man after administration of exogenous human leukocyte interferon. J. Natl. Cancer Inst. 54: 1045, 1975.
50. Gutterman, J.U., Fine, S., Quesada, J., Horning, S.J., et al. Recombinant leukocyte A interferon: pharmacokinetics, single-dose tolerance, and biologic effects in cancer patients. Ann. Intern. Med. 96: 549, 1982.
51. Rohatiner, A.Z.S., Prier, P.F., Burton, A.L., et al. Central nervous system toxicity of interferon. Br. J. Cancer 47:419, 1983.

APPENDIX I

SCHEMATIC OF MALE GENITALIA TO INDICATE LESION LOCATION

Schematic of the
Male Genitalia



	Glans	Dorsal Shaft	Ventral Shaft	Anterior Scrotum	Posterior Scrotum	Exposed Prepuce	Occluded Prepuce	Perianal
No. of Lesions								
Surface Involvement								

APPENDIX III

PROCEDURE FOR COLLECTING AND FORWARDING CONDYLOMATA TISSUE SAMPLES

Note: Degradation of the DNA occurs if the excised tissue is not snap frozen immediately (as soon as possible) after removal.

The purpose of obtaining biopsies of the condylomata during the course of interferon therapy is to examine and quantify the papillomavirus genome present in the lesion as an aid in the assessment of disease. There are at least four different subtypes of human papillomavirus type 6 in genital warts which are distinguishable by hybridization analysis. It is possible to determine the number of copies of the papillomavirus genome per cell and we can therefore monitor the impact of interferon on replication of the virus. We also will be able to correlate viral subtype with resistance or sensitivity to interferon. In addition, since the patients are being selected from different regions of the United States, these studies will indicate if there are different viruses circulating in different geographic locations. Specimens will be collected prior to and during the course of interferon. For a successful analysis, it is necessary to snap freeze the tissue (not in saline) in liquid nitrogen as soon as possible after surgical excision.

1. Biopsies, collected in saline, should be removed from the saline and placed in a labelled Nunc vial or any similar small, sterile container which can withstand liquid nitrogen.
2. The vial is to be dropped in liquid nitrogen to snap freeze the tissue and then store at -70°C .
3. Tissue specimens are to be shipped with dry ice via Federal Express or Purolator to Burroughs Wellcome Co.

BODY SURFACE AREA (m²)
POUNDS/INCHES

THPR/84/0074
P20-15/W2/48

APPENDIX IV B

BODY SURFACE AREA (m²)

KILOGRAMS/CENTIMETERS

Height (cm)	Weight (kg)																			
	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	44
50	0.25	0.31	0.36	0.40	0.44	0.48	0.51	0.54	0.57	0.60	0.63	0.66	0.68	0.71	0.73	0.75	0.78	0.80	0.82	0.86
55	0.26	0.32	0.37	0.42	0.46	0.50	0.53	0.57	0.60	0.63	0.66	0.68	0.71	0.74	0.76	0.78	0.81	0.83	0.85	0.90
60	0.27	0.33	0.39	0.43	0.48	0.52	0.55	0.59	0.62	0.65	0.68	0.71	0.74	0.76	0.79	0.81	0.84	0.86	0.88	0.93
65	0.28	0.34	0.40	0.45	0.49	0.53	0.57	0.61	0.64	0.67	0.70	0.73	0.76	0.79	0.82	0.84	0.87	0.89	0.91	0.96
70	0.29	0.36	0.41	0.46	0.51	0.55	0.59	0.63	0.66	0.69	0.73	0.76	0.79	0.81	0.84	0.87	0.89	0.92	0.94	0.99
75	0.30	0.37	0.42	0.48	0.52	0.57	0.61	0.64	0.68	0.71	0.75	0.78	0.81	0.84	0.87	0.89	0.92	0.95	0.97	1.02
80	0.31	0.38	0.44	0.49	0.54	0.58	0.62	0.66	0.70	0.73	0.77	0.80	0.83	0.86	0.89	0.92	0.95	0.97	1.00	1.05
85	0.31	0.39	0.45	0.50	0.55	0.60	0.64	0.68	0.72	0.75	0.79	0.82	0.85	0.88	0.91	0.94	0.97	1.00	1.02	1.08
90	0.32	0.40	0.46	0.51	0.56	0.61	0.65	0.70	0.73	0.77	0.81	0.84	0.87	0.91	0.94	0.97	0.99	1.02	1.05	1.10
95	0.33	0.40	0.47	0.53	0.58	0.63	0.67	0.71	0.75	0.79	0.83	0.86	0.89	0.93	0.96	0.99	1.02	1.05	1.07	1.13
	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	48	52	56
100	0.59	0.64	0.68	0.73	0.77	0.81	0.84	0.88	0.91	0.95	0.98	1.01	1.04	1.07	1.10	1.13	1.15	1.21	1.26	1.30
105	0.60	0.65	0.70	0.74	0.78	0.82	0.86	0.90	0.93	0.97	1.00	1.03	1.06	1.09	1.12	1.15	1.18	1.23	1.28	1.33
110	0.61	0.67	0.71	0.76	0.80	0.84	0.88	0.92	0.95	0.99	1.02	1.05	1.08	1.11	1.14	1.17	1.20	1.25	1.31	1.36
115	0.63	0.68	0.73	0.77	0.81	0.86	0.89	0.93	0.97	1.00	1.04	1.07	1.10	1.13	1.16	1.19	1.22	1.28	1.33	1.43
120	0.64	0.69	0.74	0.79	0.83	0.87	0.91	0.95	0.99	1.02	1.06	1.09	1.12	1.15	1.19	1.22	1.24	1.30	1.36	1.41
125	0.65	0.70	0.75	0.80	0.84	0.89	0.93	0.97	1.00	1.04	1.07	1.11	1.14	1.17	1.21	1.24	1.27	1.32	1.38	1.43
130	0.66	0.71	0.77	0.81	0.86	0.90	0.94	0.98	1.02	1.06	1.09	1.13	1.16	1.19	1.23	1.26	1.29	1.35	1.40	1.46
135	0.67	0.73	0.78	0.83	0.87	0.92	0.96	1.00	1.04	1.07	1.11	1.15	1.18	1.21	1.25	1.28	1.31	1.37	1.43	1.48
140	0.68	0.74	0.79	0.84	0.89	0.93	0.97	1.01	1.05	1.09	1.13	1.16	1.20	1.23	1.26	1.30	1.33	1.39	1.45	1.50
145	0.69	0.75	0.80	0.85	0.90	0.94	0.99	1.03	1.07	1.11	1.14	1.18	1.22	1.25	1.28	1.32	1.35	1.41	1.47	1.53
	30	34	38	42	46	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106
150	1.12	1.20	1.27	1.34	1.40	1.46	1.52	1.58	1.63	1.69	1.74	1.79	1.84	1.88	1.93	1.98	2.02	2.07	2.11	2.15
155	1.14	1.21	1.29	1.35	1.42	1.48	1.54	1.60	1.65	1.71	1.76	1.81	1.86	1.91	1.96	2.00	2.05	2.09	2.14	2.18
160	1.15	1.23	1.30	1.37	1.44	1.50	1.56	1.62	1.68	1.73	1.78	1.84	1.89	1.94	1.98	2.03	2.08	2.12	2.17	2.21
165	1.17	1.25	1.32	1.39	1.46	1.52	1.58	1.64	1.70	1.75	1.81	1.86	1.91	1.96	2.01	2.06	2.10	2.15	2.19	2.24
170	1.18	1.26	1.34	1.41	1.48	1.54	1.60	1.66	1.72	1.78	1.83	1.88	1.94	1.99	2.04	2.08	2.13	2.18	2.22	2.27
175	1.20	1.28	1.35	1.43	1.49	1.56	1.62	1.68	1.74	1.80	1.85	1.91	1.96	2.01	2.06	2.11	2.16	2.20	2.25	2.30
180	1.21	1.29	1.37	1.44	1.51	1.58	1.64	1.70	1.76	1.82	1.88	1.93	1.98	2.04	2.09	2.13	2.18	2.23	2.28	2.32
	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116
185	1.42	1.49	1.56	1.63	1.69	1.75	1.81	1.87	1.93	1.98	2.03	2.08	2.13	2.18	2.23	2.28	2.33	2.37	2.42	2.46
190	1.44	1.51	1.58	1.65	1.71	1.77	1.83	1.89	1.95	2.00	2.06	2.11	2.16	2.21	2.26	2.31	2.35	2.40	2.44	2.49
195	1.45	1.53	1.60	1.67	1.73	1.79	1.85	1.91	1.97	2.02	2.08	2.13	2.18	2.23	2.28	2.33	2.38	2.43	2.47	2.52
200	1.47	1.54	1.62	1.68	1.75	1.81	1.87	1.93	1.99	2.05	2.10	2.15	2.21	2.26	2.31	2.36	2.40	2.45	2.50	2.54
205	1.49	1.56	1.63	1.70	1.77	1.83	1.89	1.95	2.01	2.07	2.12	2.18	2.23	2.28	2.33	2.38	2.43	2.48	2.52	2.57
210	1.50	1.58	1.65	1.72	1.79	1.85	1.91	1.97	2.03	2.09	2.14	2.20	2.25	2.30	2.36	2.41	2.45	2.50	2.55	2.60
215	1.52	1.59	1.67	1.74	1.80	1.87	1.93	1.99	2.05	2.11	2.17	2.22	2.27	2.33	2.38	2.43	2.48	2.53	2.58	2.62
220	1.53	1.61	1.68	1.75	1.82	1.89	1.95	2.01	2.07	2.13	2.19	2.24	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65

APPENDIX V

PATIENT INFORMATION/INSTRUCTIONS FOR A PHASE III/IV TREATMENT OF HERPES VIRUS INFECTIONS WITH ZOVIRAX® (ACYCLOVIR) OR CONDYLOMA ACUMINATA WITH WELLFERON® (HUMAN LYMPHOBLASTOID INTERFERON) IN PATIENTS WITH UNEXPLAINED LYMPHADENOPATHY SYNDROME

INTRODUCTION

Interferon is a substance made by the body in response to a virus infection that limits its spread. Interferon's ability to decrease the size of tumors has also been noted. Both of these areas are currently being studied. WELLFERON (or human lymphoblastoid interferon produced by Burroughs Wellcome Co.) is a type of interferon being used in the study you may participate in for genital warts (or Condyloma acuminata). This is an investigational agent but so far there have been many patients participating in many different studies using WELLFERON. The earlier studies with WELLFERON have provided important information about safe doses, ways to give it and side effects that can be expected. Studies are now looking at how effective WELLFERON is with a variety of viral diseases and cancers.

The purpose of this study is to measure the efficacy of interferon in treating resistant/recurrent condyloma acuminata or acyclovir in treating primary or recurrent herpes simplex or zoster in patients with LAS.

TREATMENT PLAN

If you decide to participate in this study, you will be randomized to receive either ZOVIRAX (Regimen A) for primary or recurrent herpes simplex/zoster infection or WELLFERON (Regimen B) for resistant/recurrent condyloma acuminata (genital warts).

REGIMEN A - ZOVIRAX FOR HERPES SIMPLEX/ZOSTER

If you have been assigned to this arm of the study, you will receive ZOVIRAX 800 mg or 400 mg tablets to be taken by mouth. ZOVIRAX will be administered as one 800 mg tablet every 4 hours daily for 16 days followed by one 400 mg tablet every 8 hours daily for 4 weeks.

Following six weeks of treatment, you will be observed for 4 weeks to document regression or recurrence of herpes simplex/zoster lesions.

REGIMEN B - WELLFERON® FOR CONDYLOMA ACUMINATA (GENITAL WARTS)

If you have been assigned to this arm of the study, you will receive WELLFERON by subcutaneous (under the skin) injections at a dose of 3 Mu/m² daily for 14 days followed by the same dose given 3 times per week for 4 weeks. Subcutaneous administration will be achieved by rotation of sites on the anterior aspect of the thigh or upper arm in a volume of 0.5-1.5 ml per site. Following this 6-week period, all patients will be observed for 4 weeks to document regression or recurrence of disease.

ADDITIONAL TREATMENT OF DISEASE

Second Course of Therapy

If you experience a partial response during the initial 6-week treatment period and/or recurrence disease while undergoing observation for 4 weeks, you are eligible to receive a second 6-week course of WELLFERON or ZOVIRAX® as appropriate for your disease.

COMBINED INTERFERON AND ACYCLOVIR THERAPY

All patients experiencing no response (NR) to ZOVIRAX for Herpes viral infections or to WELLFERON for condyloma acuminata during the initial 6-week treatment and observation periods will be eligible for combined therapy. Nonresponders will receive ZOVIRAX as one 400 mg tablet every 8 hours daily for six weeks concomitant with WELLFERON subcutaneously at 3 Mu/m²/injection 3 x weekly for 6 weeks.

CROSSOVER TO OTHER TREATMENT ARM

Any patient developing disease (either HSV viral infection or condyloma acuminata) other than their original diagnosis at any time during the course of study may crossover to the treatment arm appropriate for that disease.

If at any time you wish to withdraw from the study for any personal reasons, you may do so after talking with your doctor. You will still get the best care possible no matter what you decide.

STUDIES TO BE DONE

You will be followed every week at first and then every other week by either the staff here or your family doctor. While receiving WELLFERON®, certain tests will need to be done to monitor your response and for potential side effects. This will include blood tests, photographs and check-ups. The tests and when they will be done are listed below:

Tests While Receiving ZOVIRAX® (Regimen A) or WELLFERON (Regimen B)

Date

Week of Treatment	Entry	2	3	5	7	9	11	13	15	17
Checkup (includes photographs)	X		X	X	X	X	X	X	X	X
Blood work	X	X	X	X	X	X	X	X	X	X

POSSIBLE SIDE EFFECTS AND WHAT TO DO ABOUT THEM

ZOVIRAX (Regimen A)

ZOVIRAX has no significant side effects, other than occasional single episodes of nausea or diarrhea in patients studied to date. Controlled clinical trials also have not produced evidence of acute toxicity results from oral administration of acyclovir.

WELLFERON Regimen B

WELLFERON has been given to many patients and certain effects have been observed with them. At the dose you will be receiving these generally have been very mild. There are some variations however in how people respond, even at the same dose. Most symptoms have gone away once the treatment has stopped.

It is important for you to tell us if you have any problems. You will be asked to maintain a daily dairy of symptoms and interferon injections. You can write how you are feeling and what makes you feel better or worse. Bring this in with each visit. You will also be asked to

record some things, like your temperature or weight. Your nurse will go over this with you. Below is a list of some of the side effects you may experience and what you can do about them. Remember: not all patients experience all of these side effects.

The most commonly experienced side effect include a flu-like syndrome with fever, chills, and muscle aches. This is usually the worst with the first treatment and tends to get better as time goes on. They usually don't last for more than the treatment day. You may take acetaminophen (Tylenol, Datril, etc.) for relief of these symptoms. DO NOT TAKE ANY ASPIRIN OR ASPIRIN CONTAINING PRODUCTS (read the labels) unless approved by your doctor. It is important, especially on treatment days, to drink lots of liquids. It doesn't matter what kind (as long as it's not alcoholic) and that you drink at least 2 quarts. You should take your temperature and write it down on treatment days in the afternoon, evening and at bedtime. If you don't have a thermometer or know how to read one ask your nurse.

Many people lose their appetite and this may become more noticeable as time goes on. Check your weight and write it down at least once a week. Talk with your nurse or the dietician if you have problems with this.

Feeling tired is another common problem which usually gets better when the treatment is stopped. Try to rest when you feel this way. You may want to do things that are more important to you when you have more energy such as in the morning or after resting or on days you are not taking your treatments. If this really interferes with your activities, let your doctor or nurse know about it. It may be helpful to have someone accompanying you on your treatment days.

Other possible side effects may include changes in blood counts or chemistries. That is why it is important to get the blood tests when they are ordered. This usually has not been harmful and has gotten better when the treatment has been adjusted or stopped. Possible effects of lowered white cell or platelet counts may make someone more susceptible to infection or easy bleeding or bruising. It is important to let your doctor or nurse know if you notice any of those symptoms.

REMEMBER: IT IS IMPORTANT TO NOTIFY YOUR DOCTOR OR NURSE IF YOU EXPERIENCE ANY OF THE FOLLOWING:

- fevers above 102°F not relieved by Tylenol
- severe headache lasting more than 24 hours
- any unusual bruising or bleeding
- long lasting pain or swelling at the injection site
- any sign of infection such as redness, swelling or pain
- severe tiredness
- uncontrollable vomiting or diarrhea
- any other unusual situation that you want to discuss.

DO NOT TAKE ANY OTHER MEDICATIONS WHILE RECEIVING WELLFERON® UNLESS APPROVED BY YOUR DOCTOR OR NURSE.

Interferon is an extremely potent substance and may have serious side effects. Certain conditions may lower your tolerance to some of these. It is important to let your doctor know if you have any of the following:

- high blood pressure
- heart problems
- respiratory problems (such as pneumonia or emphysema)
- liver problems
- kidney problems
- seizures
- generally weakened condition.

Your doctor or nurse will be available to discuss this in more detail if you have any questions or concerns.

CONSENT FORM

Any investigational study involving humans must go through a strict review process, required by law, at your hospital. You will be asked to sign a consent form after reviewing the treatment plan and possible effects of WELLFERON. It is helpful to have a family member with you during this discussion. You may also wish to keep a copy of the consent form. If you have any questions or concerns do not hesitate to call:

Doctor _____ at _____ or

Nurse _____ at _____.

Notes/Questions:

APPENDIX VI

NURSING INFORMATION/INSTRUCTIONS FOR A PHASE III/IV STUDY IN THE TREATMENT OF HERPES SIMPLEX/ZOSTER VIRUS INFECTIONS WITH ZOVIRAX® (ACYCLOVIR) OR CONDYLOMA ACUMINATA WITH WELLFERON® (HUMAN LYMPHOBLASTOID INTERFERON) IN PATIENTS WITH UNEXPLAINED LYMPHADENOPATHY SYNDROME

This "fact sheet" has been developed to be used as a quick reference or guide for your convenience. For more detailed information, please refer to the protocol section identified and/or the Investigator's Manual.

Purpose of Study (Section 1.0):

- a) To determine response patterns of condyloma acuminata of LAS patients to 6 weeks of treatment with human lymphoblastoid interferon (WELLFERON).
- b) To characterize response of herpes simplex virus (HSV) infections in LAS patients to oral acyclovir (ZOVIRAX) administration.
- c) To determine the tolerance and toxicity of acyclovir and human lymphoblastoid interferon in patients with LAS.
- d) To measure response rates and patterns of recurrent/resistant condyloma acuminata or recurrent HSV infections to second six-week course of human lymphoblastoid interferon or acyclovir, respectively.
- e) To determine the effectiveness of combined acyclovir and interferon treatment for disease that does not respond to initial acyclovir or interferon therapy alone.
- f) To study the molecular virology of HSV and condyloma acuminata which do and do not respond to acyclovir or interferon therapy.

Patient Eligibility (Section 3.1): Patients must have lymphadenopathy with pathologic, clinical appearance (1-3 cm diameter) and involving at least two regional chains above diaphragm. Lymphadenopathy must have been present for > 4 months duration with biopsy proven follicular hyperplasia and absence of involution and malignancy. In addition, the patient must have a diagnosis of condyloma acuminata, herpes simplex type II or herpes zoster. Condyloma must have been present for $\geq$ 3 months with at least 2 previous podophyllin or equivalent treatments. All patients must have measurable condyloma, herpes or zoster lesions. A signed informed consent is required for all patients entered into the study.

Patients with any of the following are not candidates for this study:
< 18 years old, patients with AIDS or oral candidiasis, immunological therapy within previous 3 months, serum creatinine > 1.4, hemoglobin < 10, platelet count < 100,000, WBC $\leq$ 1500, SGOT > 3 x the upper limits of normal, clinical or laboratory coagulopathy, known hypersensitivity to neomycin or Polymyxin B, receiving steroids, cytotoxic immunosuppressive agents or radiotherapy.

Treatment Plan (Section 3.0):

Eligible LAS patients with resistant/recurrent condyloma acuminata or herpes simplex lesions will have entry and eligibility forms completed. Patients will then be assigned to receive ZOVIRAX® (Regimen A) or WELLFERON® (Regimen B). Assignments will be made on the basis of the original disease diagnosis. All patients must meet the entry criteria for the syndrome of unexplained generalized lymphadenopathy.

Regimen A - ZOVIRAX for Herpes Simplex II or Herpes Zoster

Patients assigned to this arm will receive ZOVIRAX orally as 800 mg or 400 mg tablets. ZOVIRAX will be administered as one 800 mg tablet q 4 hrs daily for 14 days followed by one 400 mg tablet q 8 hrs daily for 4 weeks.

Following six weeks of treatment, all patients will be observed for 4 weeks to document regression or recurrence of herpes simplex or zoster lesions.

Regimen B - WELLFERON® for Condyloma Acuminata

Patients assigned to this arm of the study will receive WELLFERON by subcutaneous injections at a dose of 3 Mu/m² daily for 14 days followed by the same dose given 3 times per week for 4 weeks. Following this six-week period, all patients will be observed for 4 weeks to document regression or recurrence of disease..

Additional Treatment of Disease

All patients experiencing a partial response during the initial 6-week treatment period and/or recurrence of disease while undergoing observation for 4 weeks are eligible to receive a second 6-week course of WELLFERON or ZOVIRAX® as appropriate for their disease.

Any patient experiencing a complete regression and then recurrence of disease while off therapy is eligible for the second 6-week course of WELLFERON or ZOVIRAX.

Combined Interferon and Acyclovir Therapy

All patients experiencing no response (NR) to ZOVIRAX for herpes viral infections or to WELLFERON for condyloma acuminata during the initial 6-week treatment and observation periods will be eligible for combined therapy.

Nonresponders will receive ZOVIRAX as one 400 mg tablet q 8 hrs daily for six weeks concomitantly with WELLFERON subcutaneously at 3 Mu/m²/injection 3 x weekly for 6 weeks.

Crossover to Other Treatment Arm

Any patient developing disease (either HSV infection or condyloma acuminata) other than their original diagnosis at any time during the course of study may crossover to the treatment arm appropriate for that disease.

Route of Administration: Subcutaneous (S.C.) on the anterior aspect of the thigh in a volume of 0.5-1.5 ml per site. The injection sites should be rotated.

Formulation: WELLFERON is supplied in 1.0 ml sequentially numbered vials. Each vial contains approximately 5 Mu/1.0 ml but the precise unitage for each lot must be verified on the carton label.

Storage and Stability: WELLFERON® should be stored in a freezer that can reach -20°C temperatures and must not be refrozen once thawed. Since this preparation does not contain a preservative, WELLFERON may be stored for up to 48 hours in the refrigerator at 4°C if entered under a laminar flow cabinet. Thawed but unentered vials may be stored for up to one month refrigerated. The tear-off label from the vial must be attached to the Clinical Trial Material Inventory Control Form. All unused and empty drug vials must be returned to Burroughs Wellcome.

Studies To Be Done (6.0).

Please make sure that all the studies to be done are obtained when requested and are reflected in the Data Collection Forms. A notation should be made in the DCF if the study to be done was not obtained and a notation made as to why.

Protocol Requirements (Section 10.0): Individual Data Collection Forms must be filled out for each patient. Please make sure that all the studies obtained are reflected on the DCFs especially lesion measurements on the diagrams.

Toxicity Management for Acyclovir (Section 4.2.5): No significant side effects, other than occasional single episodes of nausea or diarrhea, have been observed in patients studied to date. Controlled clinical trials also have not produced evidence of acute toxicity resulting from oral administration of acyclovir.

Toxicity Management for WELLFERON (Section 7.0): Side effects should be evaluated for type, character, duration, intervention (if any) and effectiveness. This should be documented in the DCF. Although the known toxicities and suggested management for WELLFERON is listed below, the degree of individual response is highly variable and the nurse must remain vigilant for new, as yet unreported side effects of WELLFERON.

The following section outlines side effects and suggested nursing interventions for the patient receiving WELLFERON. Some of these side effects may occur simultaneously and acutely, such as the flu-like syndrome, while others appear to be more cumulative, like anorexia and fatigue. Patients may interpret side effects of the WELLFERON therapy as signs of progressive disease and they need to understand that most of the side effects are reversible upon cessation of therapy.

1. Fever is seen in about 90% of patients but is generally very mild at the doses utilized in this protocol. Any 1°C elevation is considered a febrile response. The first treatment is usually the highest with diminution or disappearance as therapy continues. However, if the treatment schedule is interrupted for a 2 to 3 day period, this may recur. Chills usually accompany the fever and may be mild or rigorous.
 - Maintain intake above 3 liters per day to prevent dehydration
 - Monitor intake and output if clinically indicated
 - Acetaminophen q. 4 hours or p.r.n. (NO ASA OR NSAID PRODUCTS ALLOWED EXCEPT WHEN PRESCRIBED BY THE PROTOCOL)
 - Have patient wear socks and/or hats if chilled
 - Have extra blankets available, if chilled
 - Use cool sponging for temperatures above 103°F
 - Have hypothermia blanket available for temperatures above 105°F
 - Monitor for cardiovascular changes; observe for changes in vital signs, chest pain or irregular pulses
 - Monitor for CNS changes including somnolence, confusion, difficulty concentrating or paying attention or seizures
 - Monitor vital signs as requested by protocol or more often if clinically indicated.
2. Myalgias and Headaches are seen in approximately 20 and 33% of the patients, respectively. These tend to be mild and short term with resolution as treatment continues.
 - Acetaminophen q. 4 hours or p.r.n. (with Tylox or Percoset if more severe)
 - Cool compresses on forehead may be comforting for a headache
 - Heat and/or massage may provide temporary relief of myalgias
 - Darken room if photophobia develops
3. Fatigue is experienced in about 52% of patients, but on the dosage used in this protocol it is generally very mild. This tends to be cumulative and may interfere with activities of daily living including sexual activity.
 - Instruct patient to arrange most important activities after rest periods

- Encourage rest periods p.r.n.
 - Encourage patient to maintain mobility as much as possible to prevent sequelae from prolonged bedrest
 - Instruct family about potential changes and management
 - Counsel patient about potential alterations in sexual activity
4. Anorexia and weight loss is experienced by 52% of patients. This appears to be cumulative. Nausea and vomiting is experienced by about 40% of patients and diarrhea is occasionally seen. But these tend to be more short term and are minimum in patients on low doses of WELLFERON®.
- Monitor weight regularly at each visit
 - Use antiemetics, antidiarrheals as needed
 - Instruct patient and family on ways to increase caloric and protein intake, use of small frequent feedings, need to continue p.o. intake despite anorexia
 - Encourage p.o. intake to 2-3 liters per day
 - Dietary consult p.r.n.
5. CNS Changes may include confusion in 9% of patients, somnolence and seizures and occasional dizziness in 10% of patients. Some CNS changes may be subtle and are easily overlooked unless evaluated carefully.
- Have baseline neurologic and mental status documented
 - Listen for subtle comments by family or patient
 - Question patient
 - Test mental status periodically when indicated
6. Leukopenia is seen in 3% of patients or Thrombocytopenia in 30% of patients have been reversible upon adjustment or cessation of WELLFERON. Significant infection or bleeding has not been reported.
- Instruct patient to report signs or symptoms of bleeding or infection
 - Assess respiratory, urinary, integumentary systems for possible infection or bleeding
 - Bleeding precautions if platelet count is $<50,000 \text{ mm}^3$
 - Infection precautions if granulocyte count is $<500 \text{ mm}^3$
7. Hypotension/Hypertension is seen in 28% of patients and may occur on the first or subsequent dose. Any rise or fall $>20 \text{ mm Hg}$ should be monitored and reported.

Patient Information:

Patient Name: .

WELLFERON® Administration:

Dose = Mu (Mu/m^2) IM = cc per vial

Day(s)/Date(s) =

Acylcovir Administration:

Dose =

Day(s)/Date(s) =

Studies to be Done (include Date/Type/Specific Instructions):

Return Appointment:

(The patients should bring their interferon vials and their Data Collection Forms with them.)

Other Comments:

For Questions/Problems Contact:

WELLFERON®
SYMPTOMATIC SIDE EFFECTS
DEFINITIONS OF SEVERITY

NOTE: Toxicities not listed should simply be coded: 1 = mild,
2 = moderate, 3 = severe.

Fever (pyrexia)

- 1 = Mild - 1°C over pretreating temperature to 38.6°C
- 2 = Moderate - 38.6°C to 39.7°C
- 3 = Severe - >39.7°C

Chills

- 1 = Mild - mild to moderate shaking
- 2 = Moderate - severe shaking
- 3 = Severe - rigors (muscle contractions associated with grade two chills)

Fatigue

- 1 = Mild - 100% normal activities; feeling of fatigue
- 2 = Moderate - 50-100% normal activities; significant fatigue, lassitude, malaise
- 3 = Severe - <50% normal activities/day; extreme discomfort, depression, lethargy

Malaise [flu-like syndrome (myalgia, arthralgia)]

- 1 = Mild - <6 hours duration
- 2 = Moderate - 6-24 hours duration and/or diminished activity
- 3 = Severe - >24 hours duration and/or remain in bed

Nausea/Vomiting

- 1 = Mild - Nausea
- 2 = Moderate - Nausea and vomiting requiring medication
- 3 = Severe - Vomiting, intractable

Headache

- 1 = Mild - Brief (less than 2 hours), not requiring analgesic
- 2 = Moderate - >2 hours but less than 24 hours, or requiring analgesic
- 3 = Severe - >24 hours, with or without analgesic

Hypertension

- 1 = Mild - Change 10-20 mm Hg
- 2 = Moderate - >20, no therapy
- 3 = Severe - >20, requiring therapy

Hypotension

- 1 = Mild - Change 10-20 mm Hg
- 2 = Moderate - Change of >20, no therapy
- 3 = Severe - Change <90/60, or requiring therapy

Local Induration, Erythema (at site of injection)

- 1 = Mild - <5 mm, <24 hours
- 2 = Moderate - 5-20 mm
- 3 = Severe - >20 mm, >48 hours