Briefing Document for the Antiviral Drugs Advisory Committee

May 14, 2003

An Efficacy Supplement Describing Suppressive Therapy with Valtrex (valacyclovir hydrochloride) Caplets to Reduce the Frequency of Transmission of Genital Herpes

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TABLE OF CONTENTS

PAGE

Abbreviations

ACOG	American College of Obstretrics and Gynecology
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ASHA	American Social Health Association
BMT	Bone marrow transplant
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CMV	Cytomegalovirus
DAVDP	Division of Antiviral Drug Products
EPC	Endpoints Committee
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
HUS	Hemolytic uremic syndrome
ITT	Intent-to-treat
NDA	New Drug Application
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NNT	Number needed to treat
OR	Odds ratio
PCR	Polymerase chain reaction
SAE	Serious adverse experience
STD	Sexually transmitted disease
TK	Thymidine kinase
TMA	Thrombotic microangiopathy
TTP	Thrombotic thrombocytopenic purpura

1. SUMMARY

Overview

In this Briefing Document, GlaxoSmithKline (GSK) summarizes clinical trial results that demonstrate that Valtrex (valacyclovir hydrochloride) 500 mg once daily, when taken by immunocompetent subjects as suppressive therapy for recurrent genital herpes and when used in conjunction with safer sex counseling, significantly reduces the risk of transmission of genital herpes to an uninfected, immunocompetent, heterosexual, monogamous partner. This landmark study represents the first demonstration that an antiviral agent can interfere with the transmission of genital herpes disease.

To support the appropriate dissemination of these new data, GlaxoSmithKline has proposed revisions to the Valtrex product labeling that would state that use of Valtrex to suppress recurrent episodes of genital herpes in the source partner of a monogamous, heterosexual, immunocompetent couple also reduces the risk of transmission of HSV-2 to the susceptible partner. Importantly, the label will state that this benefit is observed in the context of safer sex counseling, which in this study included advising patients about (1) the need to abstain from sexual activity during any genital herpes outbreak, (2) the risk of transmitting HSV-2 during asymptomatic periods, and (3) the protection afforded by condoms and the need to use condoms during every sexual act. In this document, GlaxoSmithKline also outlines plans to build upon an ongoing genital herpes educational program in order to develop and disseminate information that communicates the results from this study with emphasis on the continued importance of safer sex practices when using Valtrex suppressively for the benefit of transmission reduction.

Epidemiology of Genital Herpes

Genital herpes is the most prevalent sexually transmitted disease (STD) in the United States and has the third highest incidence after chlamydia and genital warts [Cates 1999; CDC Report 2000]. Caused primarily by herpes simplex virus type 2 (HSV-2), genital herpes disease has continued to increase in prevalence in the US according to recent national surveys and represents an ongoing public health concern. The US Centers for Disease Control and Prevention (CDC) has estimated that more than 1 in 5 persons over age 12 years in the US – approximately 45 million people – are infected with HSV-2 [Cates 1999; CDC Report 2000]. More recent extrapolations based on previously published data and current trends project that the number of people in the US with genital herpes exceeds 50 million [Corey 2000]. Importantly, it is estimated that 1 – 1.5 million new cases of genital herpes occur each year [Cates 1999; CDC Report 2000; Armstrong 2001]. It is instructive to consider this high frequency of HSV-2 seropositivity and rate of new HSV-2 diagnoses in context with recent estimates of the prevalence and incidence of other STDs in the US (see Table 1). Clearly, these numbers indicate that HSV-2 infection represents a continuing health concern.

Table 1. Estimates of the Incidence and Prevalence of STDs in the US

STD	Prevalence in US (Estimated number of people currently infected)	Incidence in US (Estimated number of new cases every year)
Genital herpes	45 million [1,2]	1 – 1.5 million [1,2,3]
Human papillomavirus (genital warts/cervical infection)	20 million [1,2]	5.5 million [1,2]
Chlamydia	2 million [1,2]	3 million [1,2]
Gonorrhea	Not available [4]	650,000 [1,2]
Syphilis	Not available [4]	70,000 [1,2]
HIV/AIDS	900,000 [5]	40,000 [5]
Hepatitis B	417,000 [1,2]	120,000 [1,2]

1 Cates 1999
2 CDC Report 2000
3 Armstrong 2001
4 No recent surveys on national prevalence of gonorrhea or syphilis have been conducted.
5 UNAIDS/WHO Report 2002.

Transmission of Genital Herpes

The importance of diminishing the spread of genital herpes becomes apparent when the magnitude of the current epidemic is considered in the context of the largely 'silent' nature of transmission. The majority of HSV-2 infection is transmitted from individuals who have unrecognized clinical symptoms or who are asymptomatic but are nonetheless shedding virus between episodes [Mertz 1992]. Among HSV-2 seropositive individuals, it is estimated that only about 15% have actually been diagnosed with genital herpes [GSK data on file], primarily because most signs and symptoms go unrecognized [Cowan 1996; Fleming 1997; Wald 2000] and because the utility of serological testing has historically been limited [Ashley 1991; Koutsky 1992]. Transmission of HSV-2 from individuals with unrecognized or asymptomatic infection may be one of the primary factors behind the persistent rise in HSV-2 seropositivity in the US; seroprevalence in adults age 12 years or older was demonstrated to be nearly 22% in 1991, an increase of 30% since the previous estimate generated 13 years earlier [Fleming 1997]. This rise occurred despite concurrent efforts to educate the public about STDs and safer sexual behavior -- programs that were primarily initiated during this time in response to the growing human immunodeficiency virus [HIV] epidemic [Arvin 1997].

An important aspect of genital herpes is that transmission can occur in long-standing monogamous relationships [Mertz 1988]. Because genital HSV-2 infection persists indefinitely and is communicable for many years, perhaps for life, low rates of sexual partner change – rates that are the norm for the population as a whole – are sufficient to sustain prevalence, whereas STDs of brief duration, such as gonorrhea, are largely limited to subsets of the population with especially high rates of partner change. In addition, it is likely that most STDs are transmitted primarily by the subset of infected persons with mild or absent clinical manifestations, for the simple reason that most persons are less likely to have intercourse in the presence of genital symptoms [Mertz 1988]. HSV-2 may be transmitted to the susceptible partner after longtime sexual contact

because infection due to unrecognized or asymptomatic reactivation in the infected partner is intermittent. Thus, genital herpes can first appear in persons seemingly at low risk for a STD, such as those in mutually monogamous relationships. In addition, the initial symptoms of genital herpes may first occur months or years after infection, explaining those instances of unexpected acquisition in monogamous or sexually inactive persons [Langenberg 1989; Diamond 1999].

Although sometimes trivialized by healthcare practitioners, genital herpes can have far-reaching consequences related to the chronic nature of the disease. In addition to the physiological morbidity experienced by infected individuals during recurrences, genital herpes can cause substantial psychological stress in both the sufferer and his/her sexual partner due to ongoing concerns about the prolonged potential for disease transmission as well as potentially serious complications such as neonatal herpes and the increased risk of HIV transmission and acquisition. Clearly, there remains an unmet medical need for improved methods of intervention to reduce transmission, particularly in the setting of a stable, monogamous heterosexual relationship.

Use of Condoms for Reducing Risk of HSV-2 Transmission

Currently the only means to reduce the risk of HSV transmission are abstinence and use of barrier methods, specifically condoms, but these are not entirely effective. In one study the annual risk for transmission of HSV-2 decreased from 13.6% in those who did not use barrier methods to 5.7% in those who did ($p=0.19$), but was not eliminated [Mertz 1992]. Since transmission appears to occur most commonly from unrecognized or asymptomatic infections, an infected individual would ideally have to use condoms during every episode of sexual intercourse; this practice is unlikely, especially in monogamous heterosexual couples in long-term relationships. In one study evaluating risks associated with HSV-2 transmission, only 15% of counseled couples used condoms routinely [Mertz 1992]. In an analysis of data from a controlled trial of an HSV-2 vaccine in monogamous couples, nearly 40% of couples reported never using condoms despite counseling on safer sex practices, while only 15% reported occasional use [Wald 2001].

Antiviral Therapy for Genital Herpes

Antiviral therapy for patients with genital herpes was first introduced in 1982 with the first approval of a Zovirax (acyclovir) product in the US. In the 1990s, Valtrex (valacyclovir hydrochloride) emerged as the output of a program to develop a more extensively absorbed prodrug of acyclovir, thereby enabling less frequent administration of valacyclovir compared to Zovirax products. Valtrex Caplets were initially approved as a prescription drug in the US in 1995.

Suppressive antiviral therapy with Valtrex has previously been shown to be effective and well tolerated for suppression of recurrent genital herpes. Immunocompetent adults with ≤9 recurrent episodes per year who received Valtrex 500 mg administered once daily were significantly more likely to remain recurrence-free than a control group receiving placebo (52% vs 7% recurrence-free after 6 months treatment with Valtrex or placebo, respectively [GSK communication to FDA, 24 February 1997]; 31% vs 3% recurrence-

free after 12 months treatment with Valtrex or placebo, respectively [GSK Report BQRT/96/0001]). Valtrex has also been shown to effectively reduce virus shedding (both in terms of number of days with shedding and number of HSV DNA copies) in the presence and absence of apparent clinical symptoms of the disease [Wald 1998]. It is theorized that a decrease in this shedding rate could subsequently reduce HSV-2 transmission. Thus, it was hypothesized that effective suppressive therapy could reduce the transmission of genital herpes disease.

Study HS2AB3009

One adequate and well-controlled clinical trial, HS2AB3009, was conducted and summarized in a Supplemental New Drug Application (NDA) submitted to the Food and Drug Administration (FDA) on October 31, 2002. Protocol HS2AB3009 was a randomized, double-blind, placebo-controlled, multicenter, international study designed to evaluate the efficacy of Valtrex in reducing the risk of HSV-2 transmission within heterosexual, HSV-2 discordant couples in a monogamous relationship. A total of 1498 couples were randomized, with 1484 couples confirmed to have received study drug and included in the intent-to-treat analysis. The HSV-2 seropositive source partner, who was required to have had a history of recurrent genital herpes (9 or fewer episodes per year), was randomized (1:1) to receive Valtrex 500mg once daily or matching placebo for 8 months.

Couples were encouraged to practice safer sex (including condom use for all sexual acts and avoidance of sexual contact during a recurrent genital herpes outbreak) and were counseled on these practices at each monthly clinic visit. The HSV-2 seronegative susceptible partner was monitored for clinical and subclinical (asymptomatic) acquisition of genital herpes. Couples visited the clinic at monthly intervals and also in the event of an HSV-2 recurrence in the source partner or a suspected initial genital herpes episode in the susceptible partner. Source partners with a recurrence of genital herpes were offered open-label treatment with Valtrex 500mg twice daily for 5 days. Susceptible partners who experienced a clinical episode of HSV infection were treated with open-label Valtrex. At the completion of the double-blind phase of the study, all source partners were offered an additional 12 months of open-label suppressive therapy with Valtrex 500 mg once daily. In addition, a subset of source partners at 3 US sites participating in the double-blind phase of the study was enrolled in a substudy evaluating the efficacy of Valtrex in the suppression of HSV shedding over a 2 month period during the main trial.

Based on prospective discussions with the Division of Antiviral Drug Products (DAVDP) at FDA, the primary study endpoint was clinical evidence of a first episode of genital HSV-2 in the susceptible partner confirmed by laboratory data (culture, polymerase chain reaction [PCR] and/or serology). All suspected cases of clinical acquisition were reviewed by an Endpoints Committee (EPC) at the end of the trial. The EPC was comprised of clinical experts on genital herpes and its function was to adjudicate all suspected cases of genital herpes acquisition and determine which cases qualified as clinical, symptomatic genital herpes occurrences confirmed by laboratory results. Twenty primary endpoints representing acquisition of symptomatic, laboratory-confirmed genital herpes were corroborated by the EPC in a blinded review; this outcome was the basis of the primary efficacy analysis.

With regard to the primary study endpoint, results demonstrated that the proportion of couples with clinically symptomatic, laboratory-confirmed evidence of a first episode of genital HSV-2 infection in the susceptible partner was 2.2% in the placebo group and 0.5% in the Valtrex group (p = 0.011; odds ratio and 95% confidence interval = 0.24 [0.06, 0.76]; approximate relative risk and 95% CI = 0.25 [0.08, 0.74]). These results show a 75% reduction in the risk of transmission of symptomatic genital herpes in couples where the source partner is receiving suppressive therapy with Valtrex 500 mg once daily.

These data were supported by results from a number of secondary endpoints. The proportion of couples with overall acquisition of genital HSV-2 infection (i.e., any patient with a confirmed primary endpoint and/or HSV-2 seroconversion) in the susceptible partner was 3.6% in the placebo group and 1.9% in the Valtrex group (p = 0.054; odds ratio and 95% CI = 0.50 [0.24, 1.01]; approximate relative risk and 95% CI = 0.52, [0.27, 0.97]). These results represent a reduction of 48% in the risk of overall acquisition of HSV-2 infection in the susceptible partners of those receiving suppressive Valtrex therapy. In addition, time to transmission of symptomatic genital herpes disease was significantly delayed in the Valtrex group compared to placebo, with a difference in estimated proportions at 8 months of 1.8% (p = 0.008; 95% CI: 0.4% to 3.2%). Time to overall acquisition of HSV-2 infection was also significantly longer in the Valtrex group vs the placebo group, with a difference in estimated proportions at 8 months of 2.2% (p = 0.039; 95% CI: 0.3% to 4.2%).

A subset of source partners (n = 89) from 3 study sites participated in a 60 day substudy to assess the efficacy of Valtrex 500 mg once daily on HSV-2 shedding from the genital tract. Valtrex was associated with significant reductions in both the number of days on which virus was shed, and the quantity of virus shed. The proportion of days on which patients shed virus (mean total shedding rate) was reduced from 10.8% in the placebo group to 2.9% in the Valtrex group ($p<0.001$); significant reductions were seen in both the mean clinical shedding rate (i.e., on days when lesions were present) and the mean subclinical shedding rate (i.e., on days when lesions were not present). There was also an approximately two $\log_{10}$ (100-fold) reduction in quantity of HSV-2 shedding (copies/mL) per day in the Valtrex recipients compared with placebo recipients ($p<0.001$).

Moreover, study HS2AB3009 provided additional confirmatory evidence in a controlled setting of the previously established suppressive benefit of Valtrex in the source partner. Time to first recurrence of genital HSV-2 in the source partner was significantly shorter in the placebo group compared to the Valtrex group ($p < 0.001$), with a difference in estimated proportions at 8 months of 39% (95% CI: 34%, 44%).

Of note, the safety data collected in HS2AB3009 are consistent with the well-characterized safety profile of Valtrex in immunocompetent adults. No new safety signal was identified in this study or in a review of postmarketing surveillance reports.

In summary, the primary study endpoint, supported by a number of secondary endpoints, (including a substudy showing significant reduction of viral shedding with suppressive Valtrex therapy), demonstrates the efficacy of Valtrex, in conjunction with safer sex

counseling, in reducing the risk of transmission of HSV-2 to a heterosexual monogamous partner.

Next Steps: Product Labeling and Education

In GlaxoSmithKline's view, the reduction in transmission shown in study HS2AB3009 comprises substantial evidence of an additional benefit of suppressive therapy with Valtrex. The recently submitted Supplemental NDA requests that the labeling for Valtrex Caplets be revised to present the results of study HS2AB3009 and to state that use of Valtrex to suppress recurrent episodes of genital herpes (in the context of safer sex counseling) in the source partner of a monogamous, heterosexual, immunocompetent couple also reduces the risk of transmission of HSV-2 to the susceptible partner. GlaxoSmithKline believes that the efficacy and safety results of this study support the inclusion of additional statements in prescription drug labeling. The following statements are proposed for addition to the INDICATIONS AND USAGE section of labeling:

> "Valtrex is indicated to reduce the risk of transmission of genital herpes with the use of suppressive therapy. Safer sex practices should be used with suppressive therapy."

The labeling will also summarize study HS2AB3009 in the CLINICAL TRIALS subsection of labeling, as shown below:

> ***"Reduction of Transmission of Genital Herpes:*** A double-blind, placebo-controlled study to assess transmission of genital herpes was conducted in 1,484 monogamous, heterosexual, immunocompetent adult couples. The couples were discordant for HSV-2 infection. The source partner had a history of 9 or fewer genital herpes episodes per year. Both partners were counseled on safer sex practices and supplied with condoms for use throughout the study period. Source partners were randomized to treatment with either VALTREX 500 mg once daily or placebo once daily for 8 months.
>
> Transmission of genital herpes to the susceptible partner (as measured by the proportion of susceptible partners with clinical evidence of a first episode of genital herpes) was 2.2% (16/741) in the placebo group and 0.5% (4/743) in the group receiving VALTREX, a reduction of 75%. The proportions of susceptible partners with acquisition of genital herpes infection were 3.6% (27/741) in the placebo group and 1.9% (14/743) in the group receiving VALTREX, a reduction of 48%."

The dose of Valtrex evaluated in study HS2AB3009 (500mg once daily) has previously been approved for suppressive therapy of recurrent genital herpes in immunocompetent patients with a history of 9 or fewer recurrences per year. As confirmed in study HS2AB3009, the suppressive benefit of Valtrex is statistically significant and clinically meaningful. Additionally, the safety profile of Valtrex at this dose is supported by information from adequate and well-controlled clinical trials, as well as post-marketing surveillance. The currently approved status of suppressive therapy with Valtrex indicates that FDA has previously assessed the benefit/risk profile for suppressive use of Valtrex in

immunocompetent patients and views it to be favorable. With the recently submitted Supplemental NDA, GlaxoSmithKline has described an additional incremental benefit of suppressive therapy with Valtrex, with no change to drug-associated risks. In our view, the new information strengthens the benefit/risk assessment of suppressive therapy with Valtrex Caplets even more in favor of benefit.

GlaxoSmithKline recognizes that this Supplemental Application has implications for communication with patients and health care professionals. If the results of Study HS2AB3009 are incorporated into labeling, as proposed, they merit appropriate consideration by health care professionals for use in patient counseling. GlaxoSmithKline similarly recognizes the importance of collaborating with health care professionals, governmental agencies and public service organizations in efforts to provide educational information on genital herpes. To support proper introduction of this new information, GlaxoSmithKline plans to continue an educational program to emphasize the need for safer sex counseling and condom use in conjunction with suppressive Valtrex therapy in those patients who are candidates for suppressive therapy. Additional information on the communication plan is provided in Section 9 of this Briefing Document.

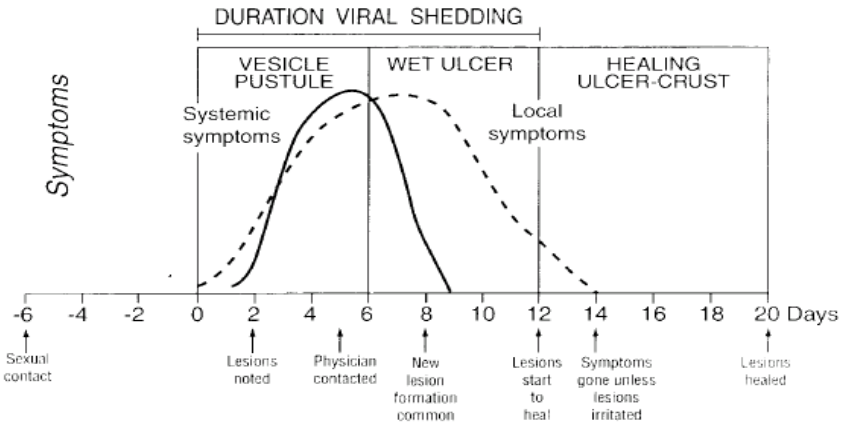
2. INTRODUCTION

Genital herpes is the most prevalent sexually transmitted disease (STD) in the US and has the third highest incidence after chlamydia and genital warts [Cates 1999; CDC Report 2000; Armstrong 2001]. Although primarily caused by herpes simplex virus type 2 (HSV-2), genital herpes is also attributed to HSV type 1 (HSV-1) [Mertz 1985, Lafferty 2000, Langenberg 1999]. Genital herpes, which is transmitted almost exclusively by sexual contact, represents a major ongoing public health concern. Reducing the risk of HSV-2 transmission is an important objective for several reasons: (1) genital herpes has physical and psychosocial morbidity, (2) genital herpes has increasing prevalence in the US, (3) transmission of genital herpes can occur "silently" during periods when the source partner is asymptomatic or has unrecognized clinical symptoms, (4) genital herpes can have serious health consequences, and (5) currently available methods for preventing HSV-2 transmission are incompletely effective. These reasons, along with challenges implicit in each, are summarized in the following sections. As noted when applicable, additional information on relevant topics is offered in the Appendices provided in Section 11 of this briefing document.

2.1. Physical and psychosocial morbidity

Genital herpes is classically described as vesicular or ulcerative lesions on the genitalia caused by HSV infection. After initial symptomatic or asymptomatic HSV infection, the virus establishes latency in the sensory ganglia and intermittently reactivates to produce recurrent genital disease or asymptomatic shedding. Prior to appearance of a lesion, erythema and edema may be present with local symptoms of itching, paresthesia or tingling. Following these prodromal symptoms, vesicles form that progress to an ulcer, which then develops a crust and heals over a period of days. A representative clinical course of a primary genital herpes infection is illustrated in Figure 1. Pain, tenderness, itching, and dysuria are symptoms that can be severe during such an outbreak [Corey 1983a and 1983b].

Figure 1. Clinical Course of Primary Genital HSV-2 Infection [1]



[1] Corey 1983a

Initial and recurrent episodes of genital herpes can be treated with antiviral drugs such as acyclovir and its prodrug Valtrex (valacyclovir hydrochloride) using episodic or suppressive dosing regimens (refer to Appendix 1 for information on the mechanism of action and approved indications for Valtrex). Despite the benefit afforded by these treatments, HSV-2 nonetheless establishes a chronic infection which is not eradicated by antiviral therapy and which can cause significant physical morbidity with recurrent episodes. In addition, considerable psychological morbidity can be experienced by both the infected individual and his/her sexual partner(s) due to feelings of anxiety, depression, isolation, frustration, aggravation concerning the recurrence of symptoms, fear of rejection and ongoing fear of transmission to a partner [Catotti 1993; Mindel 1993; Mindel 1996; Carney 1993; Carney 1994]. Furthermore, couples share concerns about potential complications of genital herpes, such as neonatal herpes (see Section 2.4 and Appendix 3). Collectively, these factors cause genital herpes to rank second only to human immunodeficiency virus (HIV) as the STD of greatest concern to sexually active individuals in the US [Catotti 1993; Handsfield 2001].

2.2. Increasing prevalence in the US

In the US, the third cycle of an ongoing, nationally representative, population-based study of health and nutrition status [National Health and Nutrition Examination Survey III, NHANES III] was conducted between 1988 and 1994 and determined that HSV-2 seroprevalence in persons 12 years of age or older living in the US was 21.9% [Fleming 1997]. This percentage corresponded to approximately 45 million infected people in 1991 and represented a 30% rise over the 13 year period since the previous survey cycle (NHANES II, conducted between 1976 and 1980) [Johnson 1989; Fleming 1997]. Considering (1) the age of the NHANES III data, (2) the chronic nature of HSV infection, (3) the fact that many HSV-1 seropositive individuals have genital infection, and (4) the trend in increasing seroprevalence, it is estimated that over 50 million persons representing approximately 25% of the adult population in the US currently have genital herpes infection [Corey 2000].

Although the NHANES III survey determined that HSV-2 seroprevalence rose in all age groups in the interval since NHANES II, particularly disturbing were the trends among the youngest age cohorts. Between 1978 and 1991, HSV-2 seroprevalence quintupled among white teenagers and doubled among whites in their twenties [Fleming 1997], indicating that a substantial number of women entering their childbearing years are infected or are at risk of acquiring infection because their partners are more likely to be infected [Arvin 1997]. Women of any ethnicity are more likely to be infected than men (25.6% vs 17.8% seroprevalence, respectively) [Fleming 1997], probably due primarily to the increased efficacy of HSV-2 transmission from men to women (see section Appendix 2). African Americans are more likely than other racial or ethnic groups to be infected, with a seroprevalence of nearly 46% in men and women combined and 55% in women alone [Fleming 1997].

Results from the fourth survey cycle, NHANES IV, are expected in 2003. It is anticipated that the rising trends in HSV-2 seroprevalence will persist, particularly among the youngest age groups studied.

2.3. Transmission of HSV-2 can occur "silently"

Transmission of HSV-2 between sexual partners is known to occur both during symptomatic and asymptomatic periods of time. Viral shedding, i.e., the presence of virus on the skin, occurs during both symptomatic and asymptomatic infections [Wald 1995; Wald 1996; Koelle 2000] and serves as a reservoir for HSV-2 transmission. The vast majority of people who have HSV-2 antibodies but do not report lesions (due to unrecognized or asymptomatic infection) nonetheless shed virus from the genital tract [Langenberg 1999]. In fact, sexual transmission of genital herpes by asymptomatic individuals has been well documented [Mertz 1985; Rooney 1986; Barton 1987]. In a study of heterosexual HSV-2 discordant couples, 70% of the transmission events took place between active outbreaks when the infected source partner was asymptomatic [Mertz 1992]. Asymptomatic viral shedding is detected in both sexes at comparable frequency [Wald 2002b]. In men, shedding can occur from the penile skin, urethra, and perianal areas, while in women it occurs from the vulva, cervix, urethra and perianal area [Wald 1995; Wald 2002b]. This broad anatomical distribution of shedding may contribute to the incomplete efficacy observed for condoms in preventing transmission of HSV-2 infection, even when they are used properly [Mertz 1992; Koelle 2000; Wald 2001]. Of note, suppressive therapy with nucleoside analogues such as Valtrex significantly reduces the frequency of asymptomatic shedding [Barton 1996; Diaz-Mitoma 1996; Patel 1997a; Sacks 1998; Straus 1996; Wald 1998; Wald 1997a]. However, it has not been established whether a threshold viral shedding rate or number of HSV DNA copies is necessary to facilitate HSV-2 transmission or to determine whether an infection will manifest as symptomatic or asymptomatic.

2.4. Serious complications of HSV-2 infection

Genital herpes can result in potentially harmful complications for the infected source partner and for newborns of pregnant women with genital herpes. The most serious direct consequence of genital HSV-2 infection is neonatal herpes, which is transmitted perinatally from an HSV-2 infected mother to her neonate [Brown 2003; Corey 2000]. When untreated, neonatal herpes has a high mortality rate (>60%) and is associated with severe neurodevelopmental impairment; however, even when treated, neurological sequelae are frequent [Whitley 1991]. The risk of transmission to neonates is highest in HSV-1/HSV-2 seronegative women who acquire HSV during the third trimester of pregnancy (1 in 1900 live births) [Brown 2003]. Current recommendations from the American College of Obstretrics and Gynecology (ACOG) call for cesarean delivery for women with first-episode or recurrent HSV infection who have active lesions or symptoms at delivery [ACOG Bulletin 2000]; these procedures result in substantially increased maternal morbidity and cost of care. (Additional information on HSV-2 infection and neonatal herpes is provided in Appendix 3).

Importantly, for the adult source partner, genital ulcer disease, including HSV-2 infection, has been identified as a risk factor for both transmission and acquisition of HIV infection [Holmberg 1991; Hook 1992]. The prevalence of HSV-2 in HIV-infected individuals or those at-risk for HIV is high [Mann 1984; Siegel 1992]. Furthermore, both symptomatic and asymptomatic HSV-2 shedding are most likely associated with cutaneous or mucosal ulceration; it is believed that ulcers need not be clinically overt to

facilitate HIV transmission or acquisition [Corey 2000]. The disease course of genital herpes can be adversely affected by HIV infection, with debilitating herpetic ulcers common in patients with AIDS; conversely, HSV-2 has also been implicated in up-regulation of HIV replication, enhancing the severity of HIV disease [Posavad 1997]. (Additional information on the interaction between HSV-2 and HIV infections is provided in Appendix 2).

2.5. Current standard of care for genital herpes

Because patients with genital herpes present with a range of signs and symptoms (and may in fact be asymptomatic), a clinical diagnosis of genital herpes based only on medical history and physical examination is often inaccurate. It is recommended that diagnosis be confirmed by further laboratory evaluation, including virologic testing (i.e., isolation of HSV in cell culture or PCR assay where available) and/or type-specific serologic testing [CDC Treatment Guidelines 2002; Handsfield 2001]. Once a diagnosis of genital herpes has been established, antiviral chemotherapy is the cornerstone of patient management. It is recommended that individuals suffering from a first episode receive antiviral treatment since symptoms may initially appear mild but can later become more severe and prolonged [CDC Treatment Guidelines 2002]. Recurrent episodes can subsequently be managed with either episodic antiviral treatment for individual outbreaks (where therapy is typically initiated upon onset of symptoms and continues for 3-5 days, depending on the antiviral agent) or with suppressive antiviral therapy to prevent recurrences. It is recommended that options for managing recurrent genital herpes episodes be discussed with all patients in order to make the most appropriate treatment decision based on an individual's physical and psychosocial needs.

In addition, patient counseling is a critical component of genital herpes disease management. According to the current CDC Treatment Guidelines [2002], counseling should have two primary goals: (1) to help the patient cope with the disease by understanding the physical and psychological consequences of infection, and (2) to educate the patient in taking steps to prevent sexual and perinatal transmission. A number of specific messages are recommended as part of the counseling effort, including advising patients about (1) the need to abstain from sexual activity during any outbreak; (2) the potential risk of transmitting genital herpes during asymptomatic periods; (3) the importance of informing current and future sexual partners of their disease status; (4) the risks of neonatal HSV-2 infection; (5) the efficacy of episodic and suppressive antiviral therapy in preventing or reducing the duration of recurrent episodes; and (6) the protection afforded by latex condoms when used consistently and correctly (CDC Treatment Guidelines 2002].

2.6. Need for improved methods for intervention of transmission

To date, increased awareness of genital herpes through education and counseling, correct and consistent use of latex condoms, and avoidance of high-risk behaviors have been the foundation of prevention campaigns. Other methods of intervention have also been investigated, such as administration of prophylatic vaccines to prevent HSV-2 acquisition and, with the completion of Study HS2AB3009, evaluation of an antiviral agent in

concert with safer sexual practices to reduce HSV-2 transmission. Before summarizing what is currently understood about the efficacy of these interventions, it is useful to review some salient points regarding the rate of HSV-2 transmission and the most important associated risk factors.

2.6.1. Rate of HSV-2 transmission

Few prospective studies have been designed and conducted in an attempt to elucidate the rate of sexual transmission of HSV-2 within serodiscordant couples. Not surprisingly, the limited available data suggest that transmission rates may vary according to the population or subgroup studied, as well as the criteria used to define acquisition. Mertz *et al* first investigated HSV-2 transmission in a subset of 144 heterosexual, HSV-2 serodiscordant couples who had been enrolled in a larger controlled trial to evaluate the efficacy of a HSV-2 subunit vaccine in preventing acquisition of genital herpes [Mertz 1992]. Participating couples, who were followed for a median of 344 days, were counseled on the risk of transmission during asymptomatic periods and on safer sexual practices, including the potential protection afforded by condoms. In this study, transmission (defined as culture-proven HSV infection or type-specific antibodies in the susceptible partner) occurred in 14 (9.7%) of 144 couples; of these 14 acquisitions, 11 (79%) occurred in female susceptible partners.

In a smaller prospective study of 57 HSV discordant monogamous couples who received safer sex counseling, the overall risk of genital HSV transmission (measured by seroconversion) was found to be 10% for each year of the relationship; all acquisitions in this study occurred in female susceptible partners [Bryson 1993].

Several large, controlled studies of candidate HSV-2 prophylactic vaccines also offer important data regarding the natural history of genital herpes acquisition. A total of 515 HSV-2 serodiscordant monogamous couples were evaluated in an 18-month study of Chiron's ineffective glycoprotein gB2/gD2 vaccine, where acquisition was defined by either seroconversion or positive genital culture [Corey 1999a]. Among these 515 couples, 28 (5.4%) susceptible partners acquired HSV-2 infection (either symptomatic or asymptomatic); of these individuals, 18 (3.5% of the total population) acquired clinically symptomatic disease. Twenty-one (75%) of the 28 total acquisitions occurred in females. In a second 18-month study evaluating this same vaccine in a higher risk population recruited from STD clinics, acquisition was observed at a similar rate, with 98 of 1753 (5.6%) susceptible partners acquiring HSV-2 infection and 39 (2.2%) acquiring clinically symptomatic genital herpes disease [Corey 1999a]. In a 19-month study conducted to investigate the efficacy of GlaxoSmithKline's glycoprotein D vaccine in susceptible partners who were both HSV-1 and HSV-2 seronegative, the overall incidence of newly acquired symptomatic genital herpes disease was 6.0% in the placebo control group, while the incidence of newly acquired infection (seropositivity) in this group was 9.2% [Stanberry 2002].

In summary, historical data from these trials of 12-18 months duration in various populations suggest that HSV-2 transmission rates range from approximately 2-4% for clinically symptomatic genital herpes disease and 5-10% for overall HSV-2 infection (both symptomatic and asymptomatic).

2.6.2. Risk factors associated with HSV-2 transmission

A number of factors can potentially influence the risk of HSV-2 transmission and acquisition. These factors, which may work independently or function interactively, include behavioral, biological and demographic characteristics. Not unexpectedly, behaviors that increase the probability of exposure to HSV-2 are generally associated with increased risk of transmission of HSV-2. Key sexual behaviors that have been associated with an increased risk of HSV-2 transmission include lack of condom use, an increasing number of sexual partners, an increasing frequency of sexual activity, and engaging in sexual activity in the presence of clinical genital herpes lesions [Siegel 1992; Cowan 1996; Wald 1997b; Wald 2001]. Biological characteristics of both the infected partner and the susceptible partner can also influence the dynamics of HSV-2 transmission and acquisition; some key biological factors associated with increased risk of HSV-2 transmission include HSV-1 serological status and concurrent HIV infection. It should also be pointed out that demographic characteristics can contribute heavily to the risk of transmission; in fact, demographic associations (such as female gender and African American ethnicity) have been observed that are stronger predictors of HSV-2 prevalence and incidence than behavioral or biological factors. It is theorized that in communities with a high HSV-2 seroprevalence, individual risk behavior is a less important predictor of STD acquisition than is demography, given that the probability of having an infected partner is very high, even among those with few partners.

A more detailed summary of key factors believed to influence HSV-2 transmission is provided in Appendix 2.

2.6.3. Methods to prevent HSV-2 transmission

2.6.3.1. Effect of condom use

The correct and consistent use of condoms has been an important factor in helping to reduce the incidence of STDs such as gonorrhea and syphilis [Casper 2002]. However, because HSV-2 can be shed over a large area of the genital region (see Section 2.3), the degree to which condoms reduce the risk of HSV-2 acquisition and transmission remains uncertain. To date, no published study has been designed specifically to determine the degree of protection offered by condoms in the acquisition or transmission of HSV-2. A recent National Institutes of Health (NIH) workshop concluded that limitations in epidemiological study designs (e.g., most trials are retrospective or cross-sectional and do not allow determination of a temporal relationship) and the lack of appropriate primary outcome measurements preclude any conclusions about the efficacy of correct and consistent use of condoms in reducing genital herpes infection [NIH Report 2001].

Many experts believe that, to date, the best measure of the effect of condom use on HSV-2 transmission and acquisition is provided by a large longitudinal study of over 500 HSV-2 serodiscordant couples who were enrolled in a candidate HSV-2 prophylactic vaccine trial [Corey 1999a]. In this study, participants were followed for 18 months with regular questionnaires assessing the frequency of sexual acts, condom use, use of acyclovir and sexual activity in the presence of active genital lesions. Although not originally designed to evaluate condom use, this study design provides considerable information regarding

the protection afforded by condoms with regard to HSV-2 acquisition. In multivariate analysis adjusted for sex, age, condom use and number of sexual acts per week, participants using condoms more than 25% of the time were less likely to acquire HSV-2 (hazard ratio [HR] = 0.25, 95% CI: 0.07-0.88) [Wald 2001]. The efficacy of condoms was especially marked in protecting women (HR=0.085; 95% CI: 0.01-0.67); the effectiveness of condoms in reducing HSV-2 acquisition in males was not demonstrated in this study, possibly due to a small number of male acquisitions. The use of condoms in preventing HSV-2 acquisition and transmission must also be viewed within the context of other factors that mediate HSV-2 transmission and acquisition (see Appendix 2 for a review of transmission-related risk factors).

2.6.3.2. Effect of prophylactic vaccines

During the 1990s several large, randomized, double-blind, placebo-controlled Phase III studies were conducted to investigate the efficacy of two promising glycoprotein vaccines in preventing acquisition of genital herpes in susceptible individuals. Two parallel Phase III studies investigated a HSV-2 glycoprotein gB2/gD2 vaccine developed by Chiron [Corey 1999a]. A total of 2268 couples were enrolled in these two 18-month, placebo-controlled studies, one of which recruited monogamous couples while the other targeted STD clinics to evaluate a higher risk population. The primary study endpoint was time to acquisition of HSV-2 infection defined by seroconversion or positive genital culture; analyses were conducted on the combined study populations. Acquisition rates were similar between vaccine and placebo recipients over the entire 18 month study period: there were a total of 126 acquisitions in both studies, representing a rate of 4.2 cases of HSV-2 per 100 person-years in the vaccine group vs. 4.6 cases in the placebo group ($P = 0.58$). The vaccine also had no significant effect on duration of first clinical HSV-2 episode or on frequency of subsequent reactivation. This vaccine was thus ineffective in reducing the rate of HSV-2 acquisition in both men and women from diverse demographic backgrounds; this finding was independent of baseline HSV-1 serostatus.

In a recent publication, Stanberry *et al* described two companion Phase III trials that evaluated a glycoprotein D subunit vaccine combined with a novel adjuvant developed by GlaxoSmithKline [Stanberry 2002]. Study 1 enrolled 847 HSV-1/HSV-2 seronegative susceptible individuals, while Study 2 enrolled 2491 subjects of any HSV serostatus; in both studies source partners had a history of genital herpes. Participants were randomized to receive vaccine or a control injection administered at months 0, 1 and 6; subjects were evaluated for 19 months. The overall incidence of newly acquired genital herpes disease in Study 1 was 3.5% in the vaccine group compared to 6.0% in the control group, while the incidence of newly acquired infection (seropositivity) was 7.1% in the vaccine group and 9.2% in the control group. These data did not show significant vaccine efficacy in preventing acquisition of genital herpes disease in this HSV-1/HSV-2 seronegative susceptible population. However, a *post hoc* subgroup analysis indicated that the vaccine demonstrated significant efficacy in preventing acquisition of genital herpes disease in female recipients but not in male subjects. Although not statistically significant, a trend was observed in protecting against acquisition of HSV infection in HSV-1/HSV-2 seronegative female subjects but not in male vaccine recipients. Similar results were demonstrated in Study 2, where the vaccine significantly reduced acquisition

of genital herpes disease in female subjects who were seronegative for both HSV-1 and HSV-2.

The greater efficacy of the GlaxoSmithKline vaccine may be due in part to its ability to induce a Th-1 type cellular immune response involving CD4 and CD8 lymphocytes, which may be more important than neutralizing antibodies alone in combating initial infection with HSV. It has been theorized that serum antibodies may be inadequate to interfere with mucosal HSV-2 infection, which establishes a regional latent infection in the absence of viremia [Mascola 1999]. In this scenario, vaccines may protect against disease but not necessarily infection; it is not known what effect such a dynamic may have on HSV-2 transmission [Stanberry 2000]. Additional research is underway to further explore the protective effect of this vaccine in a population of HSV-1/HSV-2 seronegative female subjects. However, even if efficacy of this vaccine is confirmed in this population, it will be several years before the vaccine could be available for widespread immunization.

2.6.3.3. Effect of antiviral therapy

Antiviral therapy has been shown to be effective in the treatment of first episodes and recurrent episodes of genital herpes. In addition, suppressive antiviral therapy can significantly reduce the number of symptomatic recurrences during the treatment period. Furthermore, it is known that antiviral therapy significantly decreases asymptomatic perianal and genital viral shedding. However, prior to the completion of study HS2AB3009, no data were available on the effect of antiviral therapy in reducing the risk of transmission of genital herpes within HSV-2 serodiscordant couples.

2.7. Next steps

As summarized above, it is clear that preventing the spread of genital herpes is an important public health objective. It is also apparent that there are many and varied challenges associated with this goal. An intervention that effectively reduces the risk of transmission of HSV-2 would represent an important advance in the public health sector's efforts in controlling genital herpes disease.

3. REGULATORY HISTORY OF THIS SUPPLEMENTAL APPLICATION

This supplement describes results from one large clinical trial, Study HS2AB3009; supporting data are also provided from a viral shedding substudy. Study HS2AB3009 was an international, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of Valtrex suppressive therapy of 500 mg once daily compared with placebo when administered to the source partner (the partner with HSV-2 genital herpes) in reducing the rate of transmission of HSV-2 in heterosexual, monogamous couples discordant for the presence of HSV-2. The dose of 500mg once daily is an approved dosing regimen for Valtrex for immunocompetent adults with a history of up to 9 recurrences per year, i.e., the population of source partners enrolled in this trial.

GlaxoSmithKline (GSK) has conducted antiviral drug development activities and sponsored clinical studies of genital herpes for over two decades. Some of these drug development activities have resulted in New Drug Applications and Efficacy Supplements for three antiherpetic drugs developed by the heritage companies. In the course of these development programs, we have recognized the benefits to both GlaxoSmithKline and FDA of proactive and open communication about clinical development plans and objectives. Therefore, GlaxoSmithKline has had an active dialogue with FDA about study HS2AB3009 and its underlying concepts since 1995.

We recognize the importance of and strive to utilize the opportunity afforded by a pre-study meeting between FDA and sponsor. One such meeting was conducted on September 30, 1996. There were numerous subsequent written communications and teleconferences with the Division of Antiviral Drug Products (DAVDP) that helped shape the clinical program. Prior to initiating study HS2AB3009, an active dialogue occurred between GlaxoSmithKline and FDA that included discussion of study design, patient selection criteria, selection of primary endpoint, magnitude of effect likely to be viewed as clinically significant, and other topics. This dialogue has been sustained through the tenures of Drs. Feigal, Freeman, Jolson, and Birnkrant as the senior physicians directing DAVDP.

In October 2002, when results of study HS2AB3009 became available, GlaxoSmithKline met with FDA in a pre-sNDA meeting to discuss the sponsor’s proposal to prepare an Efficacy Supplement based on this study. At this Pre-sNDA Meeting, GlaxoSmithKline obtained FDA's agreement on the format and content of the application, as well as feedback that the application would be fileable and reviewable. GlaxoSmithKline also obtained constructive feedback from the Medical Officers on some of the topics that they considered likely issues for attention in their review. Subsequently, GlaxoSmithKline submitted the Efficacy Supplement on October 31, 2002.

The remainder of this "Regulatory History" section provides FDA and the Antiviral Drugs Advisory Committee a summary of the important issues that were discussed with regard to this study. We believe that this regulatory history is useful as a means to inform the Advisory Committee of the multiyear, constructive dialogue between GlaxoSmithKline and FDA on this important topic, acknowledging the clinical study of an antiviral drug to reduce transmission of a viral sexually transmitted disease has no

direct regulatory precedent. Following this summary, we also provide a brief summary of the chronology and content of amendments to protocol HS2AB3009.

3.1. Summary of regulatory dialogue

GlaxoSmithKline and DAVDP have had an active and open dialogue since 1995 about assessment of the effect of valacyclovir on transmission of genital herpes in Study HS2B3009. It was established that changes to product labeling would be dictated by the scope and findings from the clinical program. Although many topics were discussed with DAVDP, the principal points of FDA's feedback to GlaxoSmithKline and how the issues have been addressed are summarized as follows:

1. The primary endpoint of the study must be acquisition of clinically symptomatic, laboratory-confirmed genital herpes in the susceptible partner, not seroconversion, in order to demonstrate clinical benefit to the susceptible partner. DAVDP recommended that the target patient population be HSV-2-infected source partners who are receiving suppressive therapy with valacyclovir, with monitoring of their monogamous susceptible partner for evidence of HSV-2 transmission. DAVDP advised that this study would have to yield substantial evidence of benefit to support information in labeling, i.e., a 70-80% reduction in transmission would be "strong" evidence.

   Issue addressed: The primary endpoint of Study HS2AB3009 is acquisition of clinical infection, as described above. The study was designed to detect a 75% reduction in transmission of clinical and laboratory-confirmed cases of genital herpes. This magnitude of effect is consistent with DAVDP's expectation that the study yield strong evidence of efficacy in order to enable regulatory decision making.

2. There is regulatory risk to GlaxoSmithKline associated with a plan to conduct a single, large, placebo-controlled clinical trial in a targeted population.

   Issue addressed: Since discussion began with DAVDP, a guidance was issued by FDA (Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products - May 1998) describing situations in which evidence from a single adequate and well-controlled trial can comprise substantial evidence of effectiveness. In GlaxoSmithKline's view, Study HS2AB3009 meets the standard described in the guidance document.

3. Safety concerns were expressed with the use of Valtrex in a relatively healthy, immunocompetent, adult population that may receive Valtrex as long-term suppressive therapy. A robust analysis of safety would be required.

   Issue addressed: GlaxoSmithKline has conducted three other clinical studies that collected clinical safety data in immunocompetent adults receiving Valtrex 500mg once daily (n = 706) or Valtrex 1000mg once daily (n = 269) for 8-12 months. The safety data from these studies has previously been submitted to FDA as part of the NDA for Valtrex Caplets (Studies 123-026, 123-037, 123-306; reports on these studies were submitted to FDA in a Supplemental NDA on November 18, 1996.)

These safety data, together with the safety data from Study HS2AB3009, comprise an appropriately large, multistudy source of safety data with use of Valtrex for up to 12 months. Additionally, a safety review of postmarketing data since 1995 was included in this application.

4. DAVDP advised GlaxoSmithKline of the importance of assuring that Valtrex is used in addition to safer sex counseling and condoms. DAVDP has stated the concern that an undesirable, unintended consequence of the results of Study HS2AB3009 would be an increase in higher risk sexual behaviors or use of Valtrex as an alternative to safer sex practices, including condoms.

   Issue addressed: Study HS2AB3009 was designed to provide all patients with safer sex counseling and encourage use of condoms; the effects of Valtrex vs. placebo were assessed in the setting of this counseling to all study participants. GlaxoSmithKline completely agrees that Valtrex must be used in addition to safer sex counseling and condoms. GlaxoSmithKline also agrees that an undesirable, unintended consequence of the results of study HS2AB3009 would be an increase in higher risk sexual behaviors or use of Valtrex as an alternative to safer sex practices, including condoms.

3.2. Summary of amendments to protocol HS2AB3009

Protocol HS2AB3009 was submitted to FDA as a final protocol on September 18, 1997. This submission also included Amendment # 1, which encompassed various administrative clarifications of the protocol to assure conformance with GlaxoSmithKline's Standard Operating Procedures.

Amendment # 2 to protocol HS2AB3009 was submitted to FDA on July 17, 1998. This Amendment introduced the following important changes to the protocol:

- A substudy of asymptomatic shedding was added in order to compare the effects of valacyclovir versus placebo on subclinical shedding of HSV-2 by source partners.

- The randomization visit was clarified in order to emphasize that randomization should not occur when the source partner is having a recurrent episode of genital herpes. The recurrence must resolve before the couple can be randomized into the study.

- An epidemiologic questionnaire was added to the study in order to obtain data on risk factors associated with HSV-2 seropositivity in the study population. The questionnaire was intended for administration to all source and susceptible partners screened for the study.

Amendment # 3 to protocol HS2AB3009 was submitted to FDA on December 10, 1998. This Amendment introduced a 12-month, open-label extension phase to the study. With this Amendment, any HSV-2 infected source partner in the study could (after completion of the 8 month double-blind phase of Study HS2AB3009) elect to receive open-label Valtrex 500mg once daily for an additional 12 months. This amendment enabled

GlaxoSmithKline to collect safety data for up to 20 months of continuous treatment withValtrex.

Amendment # 4 to protocol HS2AB3009 was submitted to FDA on May 25, 2000. This Amendment introduced the following changes to the protocol:

- Provisions of sample size for protocol HS2AB3009 were amended to randomize approximately 1,500 couples into the study in order to observe 28 confirmed primary endpoints. (Previously, the protocol stated its focus on the objective of randomizing 1,500 couples, without specifying a target number of endpoints.)

- The stratification ratio originally specified in the protocol according to gender and HSV-1 serological status (2:2:1:1 ratio for HSV-1 seronegative females: HSV-1 seropositive females: HSV-1 seronegative males: HSV-1 seropositive males) was amended to eliminate the requirement for a fixed number of couples within each stratum. This modification was implemented because enrollment patterns did not support this ratio and because there was no intention to analyze the data separately within strata. Randomization continued to be stratified in order to appropriately characterize study subjects and to ensure balance within strata.

- The original protocol described conduct of the study at approximately 35 study sites in the US, Canada and Western Europe. The amended protocol allowed conduct of the study at approximately 100 study sites in North America, South America, Western Europe, Eastern Europe, and Australia.

4. STUDY HS2AB3009: EFFICACY

4.1. Objectives

The objective of Study HS2AB3009 was to determine whether suppressive therapy with Valtrex (500 mg once daily) could reduce the transmission rate of genital herpes in immunocompetent, heterosexual, monogamous couples compared with placebo.

The objective of the asymptomatic shedding substudy was to determine if suppressive therapy with Valtrex could suppress asymptomatic HSV shedding compared with placebo.

4.2. Study design

Study HS2AB3009 was an international, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of Valtrex suppressive therapy compared to placebo when administered to the source partner (the partner with HSV-2 genital herpes) in reducing the rate of transmission of HSV-2 in heterosexual, monogamous couples discordant for the presence of HSV-2. Couples were stratified according to the gender and HSV-1 serological status of the susceptible partner. The HSV-2 seropositive source partner was randomized within each stratum in a 1:1 ratio to receive either Valtrex 500mg once daily or placebo for 8 months. Source partners must have had a history of ≤9 recurrences of genital herpes per year (this recurrence rate encompasses 82% of patients with genital herpes [Benedetti 1999]). In the event of a recurrence, source partners were offered open-label episodic therapy with Valtrex (500 mg twice daily for 5 days). Once this regimen was completed, source partners resumed their blinded suppressive treatment regimen. The 8 month treatment period was chosen as a sufficient duration to achieve the objectives of the study without being unnecessarily protracted. It was considered important that the study duration minimize the burden on couples who agreed to participate in this trial given the personal and intensive nature of the study and data collection and the fact that the susceptible partner was not infected. In addition, selection of this duration of treatment was supported by data from recent large, lengthy vaccine trials which suggested that the rate of HSV-2 acquisition declined over time, with more acquisitions observed during the first two 150-day intervals of the study compared to later intervals [personal communication, L. Corey 1996; data subsequently published in Corey 1999a].

The original protocol specified that couples would be recruited in a 2:2:1:1 ratio according to the randomization strata [HSV-1 seronegative females: HSV-1 seropositive females: HSV-1 seronegative males: HSV-1 seropositive males]. As it became apparent that randomization patterns did not support this ratio and as there was no intention to analyze separately within strata, the protocol was amended to eliminate the requirement for a fixed allocation of couples within each stratum. Randomization continued to be stratified in order to ensure balance within strata.

The sample size of the study was based on previous studies of monogamous heterosexual couples discordant in their HSV-2 serological status [personal communication, L. Corey

1996; data subsequently published in Corey 1999a]. A total of 28 confirmed episodes of genital HSV-2 across all strata was required to achieve 90% power to detect a 75% reduction in clinical evidence of genital HSV-2 in the susceptible partner for Valtrex compared to placebo at the two-sided 5% significance level. Based on an anticipated transmission rate of 3% for placebo, it was estimated that 750 couples per treatment arm would be required in order to observe 28 confirmed episodes.

Source partners had clinical evaluations at monthly intervals and on Days 1 and 5 of an HSV recurrence. The source partner was offered open-label treatment for recurrences that occurred during the double-blind phase of the study. Safety and tolerability of study medication were monitored by evaluating changes in hematology and clinical chemistry (randomization and Month 8 clinic visit), and by adverse event (AE) reporting at each clinic visit for the source partner.

Susceptible partners also had clinical evaluations at monthly intervals and were required to visit the clinic on Days 1, 5 and 10 of a suspected clinical first episode of HSV. The susceptible partner was treated with open-label episodic Valtrex therapy for these suspected first clinical episodes of genital herpes (1000 mg twice daily for 10 days in the US and Canada; 500mg twice daily for 5 or 10 days in other countries). Safety for the susceptible partner was assessed by reporting any serious adverse events (SAEs) that occurred during the study and by completing a hematology and chemistry assessment at Day 1 of a clinical episode of HSV-2. In addition, AEs were recorded during open-label Valtrex therapy for a suspected first episode of genital herpes.

Partners were counseled about the transmission of HSV and safer sex practices at each clinic visit. All subjects were provided with The American Medical Association's educational booklet on genital herpes titled 'Genital Herpes - A Patient Guide to Treatment' [Reitano 1997]. Condoms were offered to the couples at each clinic visit. In the US, all sites were provided with latex condoms from the same supply vendor; both spermicidal and non-spermicidal condoms were available, as were non-latex condoms for couples with a known allergy. At non-US study sites, locally available latex condoms (or non-latex condoms for those with latex allergies) were provided. A review of signs and symptoms of genital herpes episodes (including recognition of localized and systemic symptomatology) was carried out with both partners at each clinic visit with the help of standardized materials provided by the sponsor. Source partners received a diary card to record genital herpes recurrences and adverse events. Susceptible partners received a diary card to record signs/symptoms of HSV and sexual practices, including frequency of intercourse and condom use, oral and anal practices, and current sexual partners other than the study partner during each month between clinic visits. This diary card was not shared with the source partner to maintain data confidentiality.

In addition, at 4 sites in the US a subset of source partners participating in the double-blind phase of the study was also enrolled in a substudy evaluating the efficacy of Valtrex in the suppression of HSV shedding over a 2 month period during the main trial.

Successful completion of the double-blind phase of the study was defined as completion of the 8-month study period and/or clinical acquisition of HSV in the susceptible partner. Source partners had the option of enrolling in an open-label suppression phase after

successful completion of the main study, receiving an additional 12 months of Valtrex suppression therapy (500mg once daily). This open-label suppression phase, during which primarily safety data were collected, concluded in mid-March 2003; results will be provided at a later time.

Assessment of viral resistance to Valtrex/acyclovir was not included as an objective of this study or as a substudy for several reasons: (1) such measurements would have necessitated asking patients to commit to another study-related procedure (genital swabs), which was considered unduly burdensome in a trial already characterized by an intensive study schedule, lengthy time commitment and highly personal data collection; (2) another substudy (to assess viral shedding) was already included as part of the larger trial; and (3) available data do not suggest that development of drug resistance is a significant concern within the context of anti-herpetic therapy, as the prevalence of acyclovir-resistant HSV has remained low and stable despite increasing clinical use of antiviral agents directed against HSV for over two decades (see Appendix 4 for an overview of HSV resistance to acyclovir).

4.3. Study endpoints

4.3.1. Primary efficacy endpoint

The primary endpoint was the proportion of susceptible partners with clinical evidence of a first episode of genital HSV-2. Clinical evidence of a first episode was defined as symptomatic genital HSV-2 infection with laboratory confirmation. Methods of laboratory confirmation included detection of HSV-2 by culture or polymerase chain reaction [PCR] from genital swabs, or HSV-2 seroconversion. Only episodes that met these criteria, as confirmed by the Endpoint Committee (EPC)(see Section 4.4 below), were included in the analysis.

4.3.2. Secondary efficacy measures

- Time to clinical symptoms of genital HSV-2 in the susceptible partner (i.e., time to the primary endpoint) was measured as the time from randomization until first date of clinical symptoms (as confirmed by the EPC).

- Overall HSV-2 acquisition (defined as a confirmed primary endpoint and/or HSV-2 seroconversion in the susceptible partner): proportion of couples and the corresponding time to overall HSV-2 acquisition.

- HSV-2 seroconversion: proportion of couples with evidence of HSV-2 seroconversion in the susceptible partner and the corresponding time to HSV-2 seroconversion.

- Asymptomatic HSV-2 seroconversion (i.e., couples with HSV-2 seroconversion in the susceptible partner with no clinical evidence of a first episode of genital HSV-2 in the susceptible partner, as confirmed by the EPC): proportion of couples and the corresponding time to asymptomatic HSV-2 seroconversion.

- Time to first recurrence of genital HSV-2 in the source partner.
- Time to first oral HSV outbreak in the source partner.

4.4. Endpoints and Endpoint Committee

The Endpoints Committee (EPC) was comprised of extra-company experts in the field of genital herpes research, clinical evaluation and treatment, as well as a Clinical Research Physician from GlaxoSmithKline. EPC members are listed below:

Lawrence Corey, MD (University of Washington, Seattle, WA) – EPC Chairman
Zane Brown, MD (University of Washington, Seattle, WA)
Stephen Sacks, MD (Viridae Clinical Sciences, Vancouver, BC)
Raj Patel, MD (Royal South Hampshire Hospital, UK)
Dorothea Griffiths, MD, PhD (GlaxoSmithKline, Research Triangle Park, NC)

The primary purpose of the EPC was to adjudicate each endpoint case submitted by participating study sites and determine if the case qualified as an acquisition of symptomatic genital herpes infection. All cases were reviewed in a blinded manner. Each committee member was responsible for participating in the review process and providing input as to the final disposition of each case. Discussion surrounding the acceptability of a symptomatic endpoint was focused around the definition of a primary endpoint as defined in the protocol (see section 4.3.1 above). The EPC Chairman was responsible for leading discussion on each case, garnering agreement among EPC members, and documenting the EPC decision on the endpoint case report form (CRF).

All endpoint cases submitted by study investigators were reviewed by the EPC prior to database unblinding. EPC discussion regarding individual cases was based upon available information (e.g., submitted endpoint forms, relevant subject CRF pages, laboratory serology and culture data) and the clinical/scientific expertise of the EPC members. The EPC assigned a designation to each submitted case, either confirming the case as a clinical, symptomatic endpoint, identifying the case as an asymptomatic acquisition (i.e., positive HSV-2 serology but no clinical signs or symptoms), or rejecting the case as not meeting criteria for symptomatic or asymptomatic acquisition. The goal of each case review was to reach consensus; however, individual clinical expertise and subsequent opinions could vary. Therefore, majority vote of the EPC members dictated the final designation of each case. In the event of a tie, the Endpoint Committee Chairman cast the deciding vote. Once the EPC reviewed a case and reached a decision, the EPC Chairman completed the endpoint CRF. The signature of the EPC Chairman on the endpoint CRF affirmed that each case presented to the EPC was adequately discussed, and an agreement consistent with the resulting documentation was reached. The signature of the EPC Chairman also confirmed that each case review was managed in a manner consistent with the protocol.

4.5. Patient Population

4.5.1. Inclusion Criteria

Source partners had to satisfy the following criteria to be eligible for inclusion in the study:

1. 18 years of age or older
2. General good health as determined by current medical status and laboratory tests
3. Active heterosexual relationship with susceptible partner
4. Presence of HSV-2 serum antibody as determined by Western blot analysis
5. History of ≤ 9 symptomatic recurrences of genital herpes per year
6. Not receiving HSV suppressive therapy upon entering study
7. In the investigator's opinion, able to comply with protocol requirements
8. In the investigator's opinion, subjects must have been candidates for receiving suppressive therapy for management of their recurrent disease.
9. Written informed consent

In addition to criteria 1, 2, 7 and 9 above, **susceptible partners** had to additionally satisfy the following criteria to be eligible for inclusion in the study:

1. Active monogamous, heterosexual relationship with source partner
2. Absence of HSV-2 serum antibody as determined by Western blot analysis

4.5.2. Exclusion Criteria

Source partners were ineligible for inclusion in the study if any of the following applied:

1. Subjects who were known or suspected to be immunocompromised (e.g., subjects receiving immunosuppressive therapy, subjects with malignancy or seropositive for HIV)
2. Impaired renal function as defined by serum creatinine > 1.5 mg/dL (133 μM) or estimated creatinine clearance < 30 ml/min
3. Impaired hepatic function defined as an alanine transaminase (ALT) level > 3 times the normal upper limit
4. Known HSV-2 resistance to acyclovir, famciclovir, or ganciclovir
5. Known hypersensitivity to acyclovir, Valtrex, famciclovir or ganciclovir
6. Malabsorption syndrome or other gastrointestinal dysfunction that might impair drug dynamics
7. Subjects known to be lactose intolerant

8. Women contemplating pregnancy within the duration of study drug dosing for this study
9. Women of child bearing potential not using an effective method of contraception
10. Positive pregnancy test (or pregnant females or nursing mothers)

In addition to the criteria above, **susceptible partners** were ineligible for inclusion in the study if any of the following applied:

1. Subjects who had received an active HSV vaccine (subjects known to have received placebo in clinical trials were eligible)
2. Presence of symptomatic genital herpes
3. Subjects having sexual relations with anyone other than the source partner

4.6. Statistical Methods

4.6.1. Sample Size Considerations

Sample size was based on the primary efficacy endpoint. The study was designed to detect a 75% reduction in transmission rates in couples receiving Valtrex compared to placebo. In order to provide 90% power for a two-tailed test of proportions at the 5% significance level, a total of 28 confirmed episodes of genital HSV-2 across all strata was required [Shuster 1993].

Previous experience suggested that 3% of couples would show clinical evidence of genital HSV-2 disease in the susceptible partner after placebo treatment over 8 months [personal communication, L. Corey, 1996; data subsequently published in Corey 1999a]. A reduction of 75% compared to placebo would imply a transmission rate of 0.75% for Valtrex. Based on the anticipated transmission rates, it was estimated that 750 couples per treatment arm would be required in order to observe 28 confirmed episodes.

Operationally, study enrollment was terminated at 1498 couples, close to the targeted 1500. At that time, 23 suspected clinical endpoints had been identified by the EPC (via ongoing review prior to the definitive end-of-study EPC meeting) and it was projected that a further 5 endpoints would occur. However, when all 1498 couples had completed the 8 month double-blind phase, the EPC convened and, after thorough review of all available data, confirmed 20 primary endpoints rather than the originally projected 28.

4.6.2. Analysis Populations

The Intent-to-Treat (ITT) population was defined as all couples where source partners were randomized to treatment. Randomized couples were only excluded if there was clear evidence that the source partner failed to take any study medication.

4.6.3. Efficacy Analyses

4.6.3.1. Primary efficacy measure(s)

The primary endpoint was the proportion of susceptible partners with clinical evidence of a first episode of genital HSV-2. Clinical evidence of a first episode was defined as symptomatic genital HSV-2 infection with laboratory confirmation. Methods of laboratory confirmation included detection of HSV-2 by culture or PCR from genital swabs, or HSV-2 seroconversion. Only episodes confirmed by the EPC were included in the analysis. Episodes occurring in susceptible partners with positive or atypical HSV-2 serology results at randomization were excluded by the committee.

Comparisons between treatments for proportion of couples were performed using exact test for stratified 2x2 contingency tables using the test described by Gart [Gart 1970] and Cox [Cox 1966]. Stratification corresponded to the randomization and was by sex and susceptible partner's screening HSV-1 serostatus [HSV-1 seronegative females: HSV-1 seropositive females: HSV-1 seronegative males: HSV-1 seropositive males]. Since the randomization was not stratified by center, the statistical analysis was not adjusted for center. The two-sided p-value was calculated by doubling the one-sided value. An exact common odds-ratio estimate and 95% confidence interval were also calculated.

Sensitivity Analysis

A couple was considered to have missing data if the susceptible partner discontinued the study prematurely, with no confirmation of an endpoint. In the primary analysis of proportions, such couples are included as not having transmitted HSV-2. This method accords with a "last-value-carried forward" approach and with the assumption that susceptible partners who developed symptoms would present to the clinic. This handling of missing data in the primary analysis was discussed and agreed as appropriate with the DAVDP at FDA during the protocol development phase at a teleconference on November 25, 1997.

The potential sensitivity of the above analysis to different approaches to handling missing data was thoroughly explored in consultation with external experts. In summary, the following methods were used to assess the effect of missing data on the primary analysis.

a) Excluding missing data: couples with missing data were excluded from the analysis.
b) Event imputation: endpoints for couples with missing data were imputed at the placebo rate for both treatment groups.
c) Score penalty for missing data: all subjects with the endpoint were given a score of 1, subjects completing the study without an endpoint a score of 0 and those with missing data a score of the placebo rate. Analysis was performed using the extended Mantel-Haenszel test.
d) Time-to-event analysis: couples without the endpoint were included as censored at their last time point when they were confirmed not to have symptomatic HSV-2 infection.

An analysis including all discontinuations as treatment failures was not performed as this is not appropriate for a transmission trial with a low incidence of endpoints. The number of discontinuations was anticipated to be much greater than the number of observed endpoints in the primary analysis. Therefore, an analysis which includes discontinuations as transmissions would be dominated by a comparison of discontinuations. A study designed to detect a difference under these assumptions would be impossible to conduct.

4.6.3.2. Secondary efficacy measure(s)

Time to Clinical Symptoms of Genital HSV-2 by the Susceptible Partner

Time to clinical symptoms of genital HSV-2 in the susceptible partner (i.e., time to the primary endpoint) was measured as the time from randomization until first date of clinical symptoms (as confirmed by the Endpoint Committee). Times were compared between treatments using the logrank test, stratified by susceptible partner's gender and screening HSV-1 serostatus. Subjects who did not reach an endpoint had censored event-free times equal to the last day that the absence of the endpoint was confirmed through examination/serology. Kaplan-Meier graphs were plotted as an ascending curve in accordance with recent recommendations [Pocock 2002].

Other secondary efficacy measures

These measures were as follows:

- Overall HSV-2 acquisition (defined as a confirmed primary endpoint and/or HSV-2 seroconversion in the susceptible partner): proportion of couples and the corresponding time to overall HSV-2 acquisition.

- HSV-2 seroconversion: proportion of couples with evidence of HSV-2 seroconversion in the susceptible partner and the corresponding time to HSV-2 seroconversion.

- Asymptomatic HSV-2 seroconversion (i.e., couples with HSV-2 seroconversion in the susceptible partner with no clinical evidence of a first episode of genital HSV-2 in the susceptible partner, as confirmed by the EPC): proportion of couples and the corresponding time to asymptomatic HSV-2 seroconversion.

- Time to first recurrence of genital HSV-2 in the source partner.

- Time to first oral HSV outbreak in the source partner.

Proportion endpoints were analyzed as for the primary endpoint. Time-to-event endpoints were analyzed as for time to clinical symptoms of genital HSV-2 in the susceptible partner.

4.6.3.3. Subgroup analyses

The evidence for a differential effect of treatment across different subgroups was examined using interaction tests. Analyses were performed for the primary endpoint of clinical evidence of a first episode of genital HSV-2 in the susceptible partner and for overall acquisition of genital HSV-2 infection in the susceptible partner. Analyses were performed using Zelen's exact test for homogeneity of odds ratios (Zelen 1971).

4.6.3.4. Covariate analyses

Covariate analyses were performed for the primary endpoint of clinical transmissions and for overall acquisition of genital HSV-2 infection in the susceptible partner. The study was stratified by gender and susceptible partner's screening HSV-1 serostatus. Other covariates evaluated were frequency of sexual contacts, condom use, age of susceptible partner, country and duration of genital herpes in the source partner.

Analyses were performed for both proportions of subjects with the event and for time-to-event. Analysis of proportions was performed using logistic regression analysis; time-to-event analysis was performed using Cox's proportional hazards model. Because these models rely on asymptotic assumptions, a further analysis was performed using exact logistic regression.

4.6.3.5. Asymptomatic Shedding Substudy

For each subject each study day was classified a) by PCR as "shedding" or "no shedding" and b) as "clinical" (i.e., presence of genital lesions) or "asymptomatic" (i.e., no genital lesions). The total shedding rate was defined for each subject as the proportion of days for which shedding was detected by PCR; the asymptomatic shedding rate was defined as the proportion of asymptomatic days for which shedding was detected by PCR. Mean shedding rates were calculated as the mean across the separate shedding rates for each subject. Total and asymptomatic shedding rates were compared between treatment groups using a Wilcoxon test, stratified by the susceptible partner's gender and screening HSV-1 serostatus.

The proportion of subjects with at least one day of shedding was compared between treatments as for the primary endpoint using the exact test for stratified 2x2 contingency tables described by Gart [Gart 1970] and Cox [Cox 1966]. A similar comparison was made for the proportions of subjects with at least one day of asymptomatic shedding (i.e., shedding on days with no symptoms).

The average HSV DNA copy number per day was derived for each subject using the sum of the available PCR scores divided by the number of days. (A value of zero was used for days with no shedding). The average HSV DNA copy number per day for shedding days was derived for each subject with at least one day of shedding using the sum of the available PCR scores divided by the number of shedding days. Similarly, the average HSV DNA copy number per day for asymptomatic shedding days was derived for each subject with at least one day of asymptomatic shedding using the sum of the available PCR scores on asymptomatic days divided by the number of asymptomatic shedding

days. Average copy numbers were log-transformed prior to analysis and compared between treatment groups using a Wilcoxon test, stratified by the susceptible partner's gender and screening HSV-1 serostatus.

4.7. Results

4.7.1. Study Population

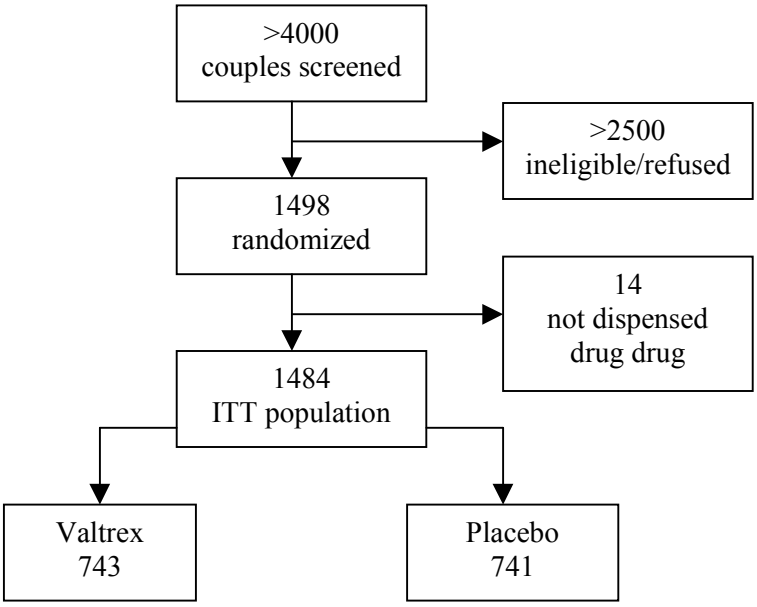
4.7.1.1. Patients screened and enrolled

Approximately 4030 couples were screened for inclusion in the study by 96 investigators at 100 sites in 21 countries over a period of 42 months. Of these 4030 couples, 1498 were randomized into the study. The primary reason for screen failure was lack of HSV-2 discordancy within couples.

4.7.1.2. Patient disposition

Of the 1498 couples randomized into the study, 1484 source partners were allocated study drug and were included in the ITT population. Of these 1484 couples, 1426 couples (96%) returned to the clinic for one or more monthly clinic evaluations. A total of 58 couples (4%) never returned for any study evaluations. A total of 741 source partners were randomized to the placebo group and 743 were randomized to receive Valtrex (the disposition of couples screened and randomized is depicted in Figure 2). The number of participating investigators was as follows: 44 in the US, 18 in Western Europe, 16 in Eastern Europe, 7 in Latin America, 6 in Canada, and 5 in Australia.

Figure 2. Disposition of Study Couples



Source partner randomization was stratified according to gender and screening HSV-1 status of the susceptible partner. Stratification variables for the ITT population, as well as the numbers recruited in each stratum, are presented in Table 2.

Table 2. Subject Stratification (ITT Population)

Population	Placebo N = 741	Valtrex N = 743	Total N = 1484
Susceptible Partner's Status			
Total Female	244 (33%)	244 (33%)	488 (33%)
HSV-1(-ve) Female	51 (7%)	52 (7%)	103 (7%)
HSV-1(+ve) Female	192 (26%)	191 (26%)	383 (26%)
HSV-1(atypical) Female	1 (<1%)	1 (<1%)	2 (<1%)
Total Male	497 (67%)	499 (67%)	996 (67%)
HSV-1(-ve) Male	176 (24%)	174 (23%)	350 (24%)
HSV-1(+ve) Male	318 (43%)	323 (43%)	641 (43%)
HSV-1(atypical) Male	3 (<1%)	2 (<1%)	5 (<1%)

The majority of susceptible partners (male and female combined) were HSV-1 seropositive (69% in each treatment group). A greater percentage of the overall number of female susceptible partners enrolled were HSV-1 seropositive (383/488, 78%) than the overall number of male susceptible partners enrolled (641/996, 64%).

Table 3 provides a summary of discontinuations for both source and susceptible partners, which were evenly distributed between the treatment groups.

Table 3. Discontinuations – Source and Susceptible Partners (ITT Population)

Discontinuations from Study, Source Partner (ITT Population)			
	Placebo N=741 n	**Valtrex N=743 n**	**Total N=1484 n**
Completed Study	575 (78%)	589 (79%)	1164 (78%)
Discontinued Prematurely	166 (22%)	154 (21%)	320 (22%)
Reason for Premature Discontinuation			
Adverse Event	5 (<1%)	11 (1%)	16 (1%)
Consent Withdrawn	54 (7%)	28 (4%)	82 (6%)
Lack of Efficacy	8 (1%)	1 (<1%)	9 (<1%)
Lost to Follow-up	38 (5%)	38 (5%)	76 (5%)
Protocol Violation	8 (1%)	8 (1%)	16 (1%)
Relationship break-up	33 (4%)	33 (4%)	66 (4%)
Relocation/travel	7 (<1%)	12 (2%)	19 (1%)
Pregnancy/attempted preg.	7 (<1%)	6 (<1%)	13 (<1%)
Partner withdrew	3 (<1%)	3 (<1%)	6 (<1%)
Other	3 (<1%)	14 (2%)	17 (1%)
Discontinuations from Study, Susceptible Partner (ITT Population)			
	Placebo N=741 n	**Valtrex N=743 n**	**Total N=1484 n**
Completed Study	577 (78%)	585 (79%)	1162 (78%)
Discontinued Prematurely	164 (22%)	158 (21%)	322 (22%)
Reason for Premature Discontinuation			
Adverse Event	0	0	0
Consent Withdrawn	46 (6%)	26 (3%)	72 (5%)
Lack of Efficacy	0	0	0
Lost to Follow-up	41 (6%)	41 (6%)	82 (6%)
Protocol Violation	8 (1%)	8 (1%)	16 (1%)
Relationship break-up	32 (4%)	40 (5%)	72 (5%)
Relocation/travel	9 (1%)	13 (2%)	22 (1%)
Pregnancy/attempted preg.	6 (<1%)	6 (<1%)	12 (<1%)
Partner withdrew	18 (2%)	15 (2%)	33 (2%)
Other	4 (<1%)	9 (1%)	13 (<1%)

The most frequent reasons for discontinuing the study for the source partner were: consent withdrawn (82 subjects), lost to follow-up (76 subjects), and relationship dissolution (66 subjects). A similar pattern of discontinuation was observed for susceptible partners. Overall, the number of subjects who discontinued from the study was similar between the Valtrex and placebo group, although more subjects in the

placebo group discontinued due to withdrawal of consent (54/741 [7%] for source partners; 46/741 [6%] for susceptible partners) compared to the Valtrex group (28/743 [4%] for source partners; 26/743 [4%] for susceptible partners).

There were 11 source partners who received Valtrex who discontinued from the study due to an adverse event. One source partner who received Valtrex stopped taking study medication due to an AE (urticarial rash) during the study period, but was not withdrawn from the study.

There were 8 couples in the study where one partner withdrew from the study, but the other partner did not. Of these 8, 3 source partners withdrew (one due to pregnancy, one due to dissolution of the relationship and one due to consent withdrawal) but the susceptible partner stayed in the study. In addition, 5 susceptible partners withdrew from the study (4 were lost to follow-up and one departed for a lengthy holiday) but their source partners remained in the study.

None of these discontinued couples had achieved a known primary endpoint at the time of withdrawal.

4.7.2. Patient demographics and baseline characteristics

4.7.2.1. Patient Demographics

Key demographic characteristics for both the source and susceptible partners are provided in Table 4.

Table 4. Demographic Characteristics (ITT Population)

	Placebo N=741	Valtrex N=743	Total N=1484
Source Partner			
Gender, n			
Female	497 (67%)	499 (67%)	996 (67%)
Male	244 (33%)	244 (33%)	488 (33%)
Age (years)			
Median (Range)	34 (19-65)	35 (18-75)	35 (18-75)
Race, n			
White	672 (91%)	666 (90%)	1338 (90%)
Black	18 (2%)	18 (2%)	36 (2%)
Asian	7 (<1%)	13 (2%)	20 (1%)
American Hispanic	41 (6%)	44 (6%)	85 (6%)
Other	3 (<1%)	2 (<1%)	5 (<1%)
Susceptible Partner			
Gender, n			
Female	244 (33%)	244 (33%)	488 (33%)
Male	497 (67%)	499 (67%)	996 (67%)
Age (years)			
Median (Range)	34 (18-76)	35 (18-74)	35 (18-76)
Race, n			
White	666 (90%)	664 (89%)	1330 (90%)
Black	20 (3%)	22 (3%)	42 (3%)
Asian	8 (1%)	10 (1%)	18 (1%)
American Hispanic	40 (5%)	40 (5%)	80 (5%)
Other	7 (<1%)	7 (<1%)	14 (<1%)

Subject demographics were similar for both source and susceptible partners across the treatment groups. There were 488 female susceptible partners (33%) and 996 male susceptible partners (67%). The majority of susceptible partners were white in both treatment groups (90% placebo, 89% Valtrex) and the median age was 34 in the placebo group and 35 in the Valtrex group.

4.7.2.2. Patient Baseline Characteristics

A summary of history of HSV infection for source partners is provided in Table 5.

Table 5. Summary of HSV History – Source Partners (ITT Population)

	Placebo N=741	Valtrex N=743
Years from Initial Episode		
N	739	740
<3 yr	209 (28%)	185 (25%)
3 - < 7 yr	171 (23%)	166 (22%)
7 - <12 yr	165 (22%)	162 (22%)
≥12 yr	194 (26%)	227 (31%)
Median	6.6 yrs	7.5 yrs
Received chronic suppressive anti-herpes therapy for >12 weeks within the previous year:		
N	741	743
Yes, n	56 (8%)	51 (7%)
No, n	685 (92%)	692 (93%)
If **Yes**, length of most recent suppressive therapy (years)		
n	18	24
Mean (range)	0.7 (0-4)	0.5 (0-2)
If on suppressive therapy, recurrence rate of <10 recurrences per year before chronic suppression?		
Yes, n	56 (100%)	51 (100%)
No, n	0	0
If **Yes (<10)**, number of recurrences per year after suppressive therapy?		
N	53	49
Median (range)	1.0 (0-9)	1.0 (0-9)
If **No**, number of recurrences in the previous 12 months?		
N	684	692
Median (range)	5.0 (0-10)	5.0 (0-10)

The two treatment groups were similar with regard to HSV history. Of note, the number of patients who had taken suppressive antiherpes therapy within the previous year was low (≤ 8%).

A summary of sexual history and practices for susceptible partners at baseline is provided in Table 6.

Table 6. Summary of Sexual History and Practices at Baseline Susceptible Partner (ITT Population)

	Placebo N=741	Valtrex N=743
Sexual relations with other partners in the 3 months prior to enrolling in the study?		
N	740	743
Yes	15 (2%)	10 (1%)
No	725 (98%)	733 (99%)
Duration of current relationship with source partner (years)		
n	735	737
<1 yr	224 (30%)	217 (29%)
1 - <3 yr	204 (28%)	223 (30%)
3 - <8 yr	166 (23%)	158 (21%)
≥8 yr	141 (19%)	139 (19%)
Median	2 yrs	2 yrs
Ever treated for a sexually transmitted disease?		
N	739	741
Yes	160 (22%)	168 (23%)
No	579 (78%)	573 (77%)
If **Yes**, which disease? n		
Genital warts	45 (6%)	41 (6%)
Chlamydia	40 (5%)	53 (7%)
Gonorrhea	35 (5%)	39 (5%)
Candida	23 (3%)	29 (4%)
Non-specific Urethritis	12 (2%)	14 (2%)
Syphilis	0	1 (<1%)
Other	35 (5%)	26 (3%)
Sexual intercourse with source partner in last month, n	740	743
Yes, n	713 (96%)	725 (98%)
No, n	27 (4%)	18 (2%)
Approximate number of sexual acts in the last month?		
n	737	739
<4	177 (24%)	174 (24%)
4 - <8	213 (29%)	207 (28%)
8 - <13	178 (24%)	214 (29%)
≥13	169 (23%)	144 (19%)
Median	6	7
Condoms Used		
n	713	725
Never (0%) n	352 (49%)	368 (51%)
Sometimes (1-90%) n	135 (19%)	128 (18%)
Nearly Always (90-100%) n	226 (32%)	229 (32%)

Twenty-five (2%) susceptible partners reported having sexual relations with partners other than their source partner in the 3 months prior to starting the study. The duration of the current relationship with their source partners was a median of 2 years in both treatment groups. Ninety-seven percent of susceptible partners reported having had sexual intercourse with their source partners in the month preceding enrollment; the median approximate number of contacts was 6 in the placebo group, and 7 in the Valtrex group. Approximately one-third of susceptible partners in both treatment groups reported use of condoms 'nearly always', while approximately one-half of susceptible partners in both the placebo and Valtrex groups reported 'never' using condoms during sexual relations in the months prior to randomization.

4.7.3. Primary efficacy result

Proportion of couples with clinical evidence of a first episode of genital HSV-2 in the susceptible partner

Clinical evidence of a first episode was defined as symptomatic genital herpes infection that was confirmed by laboratory analysis. Methods of laboratory confirmation included detection of HSV-2 by culture or PCR from genital swabs, or HSV-2 seroconversion.

As noted previously, all suspected cases of clinical acquisition were reviewed by an EPC at the end of the study. The outcome of the EPC review formed the basis of the primary efficacy analysis. Only episodes confirmed by the EPC were included in the analysis. Susceptible partners with positive or atypical HSV-2 serology results before/at randomization were not included as cases of acquisition. Seventy-one cases (42 from the placebo group and 29 from the Valtrex group) were submitted to the EPC for blinded review based on potential signs and symptoms of genital herpes and/or positive laboratory data. Of these 71 cases, 20 were subsequently determined to meet the criteria for the primary endpoint (see Figure 3 below).

Figure 3. Outcome of EPC Review of Potential Primary Endpoints

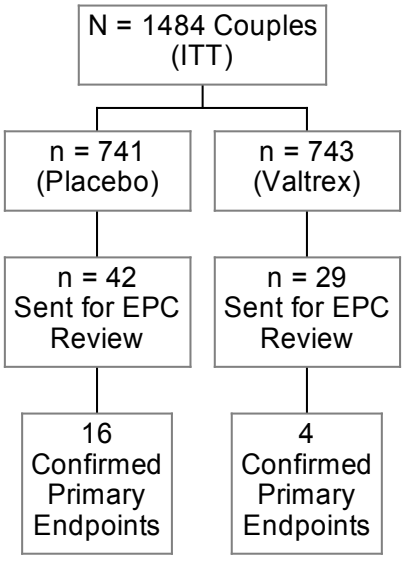


Table 7 provides a summary of the proportion of couples with clinical evidence of a first episode of genital HSV-2 in susceptible partners for the ITT Population.

Table 7. Summary of Clinical Evidence of a First Episode of Genital HSV-2 in Susceptible Partners (ITT Population)

	Placebo (N=741)	Valtrex (N=743)
Primary Analysis:		
Clinical evidence of first episode of genital HSV-2		
n	16 (2.2%)	4 (0.5%)
Odds Ratio (95% CI)		0.24 (0.06, 0.76)
p-value		0.011
Approximate Relative Risk (95% CI)		0.25 (0.08, 0.74)

The proportion of couples with clinical evidence of a first episode of genital HSV-2 infection in the susceptible partner was 2.2% (16/741) in the placebo group and 0.5% (4/743) in the Valtrex group (p=0.011, odds ratio [95% CI]: 0.24 [0.06, 0.76]; approximate. relative risk [95% CI]: 0.25 [0.08, 0.74]). A relative risk of 0.25 represents a reduction of 75% in the risk of transmission of symptomatic genital herpes.

Source partners of susceptible partners with confirmed clinical acquisitions during the study had between 0 and 12 HSV recurrences; 7 of 20 source partners had 0 HSV recurrences and one source partner had 12 HSV recurrences.

Summary of Sexual Exposure and Practices – Susceptible Partner

During the 8-month double-blind study period, the susceptible partner recorded sexual exposure and practice data on a diary card. This diary card was returned to the clinic each month and reviewed by the investigator. Information from the diary card was recorded in the case report form (CRF). This information included the number of sexual contacts (vaginal, anal, and oral) with the subject's source partner, as well as information on condom use during each sexual contact. Table 8 summarizes the sexual exposure and practice history during the study.

Table 8. Summary of Overall Sexual Exposure and Practices During the Study - Susceptible Partner (ITT Population)

	Placebo N = 741	Valtrex N = 743
Total number of vaginal sexual contacts during the study		
n	709	711
Median (range)	45 (0-482)	48 (0-336)
Condom Use[1], n (of those having vaginal sex, number of subjects answering question on condom use)	703	703
Nearly always, n	212 (30%)	211 (30%)
Sometimes, n	103 (15%)	92 (13%)
Never, n	388 (55%)	400 (57%)
Total number of anal sexual contacts during the study		
n	710	713
Median (range)	0.0 (0-73)	0.0 (0-58)
Condom Use[1], n (of those having anal sex, number of subjects answering question on condom use)	112	116
Nearly always, n	22 (20%)	29 (25%)
Sometimes, n	7 (6%)	6 (5%)
Never, n	83 (74%)	81 (70%)
Total number of oral sexual contacts during the study		
n	709	712
Median (range)	9.0 (0-298)	10.0 (0-206)
Condom Use[1], n (of those having oral sex, number of subjects answering question on condom use)	537	556
Nearly always, n	39 (7%)	38 (7%)
Sometimes, n	21 (4%)	40 (7%)
Never, n	477 (89%)	478 (86%)

[1] Nearly Always = 90-100%, Sometimes = 1-90%, Never = 0%

Patterns of condom use were similar between the Valtrex and placebo treatment groups. These data show that only about 30% of couples used condoms 'nearly always' during vaginal sexual intercourse, while the majority of couples (55-57%) reported 'never' using condoms during vaginal intercourse during the study period. Condom use therefore did not change appreciably from baseline, where susceptible partners reported using condoms 'nearly always' only 32% of the time during vaginal sexual intercourse the month prior to screening.

Of the 20 (16 placebo, 4 Valtrex) susceptible partners with confirmed endpoints, 15 (11 placebo, 4 Valtrex) reported 'never' using condoms during the study during vaginal sexual contacts; 3 (all placebo) reported using condoms 'nearly always' during the study period; 2 (both placebo) reported using condoms 'sometimes'. The number of vaginal sexual contacts reported for these subjects during the entire course of the study ranged from 2 to 296.

Of those who had anal sexual contacts during the study, only 20% in the placebo group and 25% in the Valtrex group 'nearly always' used condoms. For oral sexual contacts

during the study, only 7% of subjects in both treatment groups reported using condoms 'nearly always'.

4.7.4. Sensitivity analyses

A couple was considered to have missing data if the susceptible partner discontinued the study prematurely with no confirmation of an endpoint. Table 9 provides a summary of the length of time for which subjects were followed for the primary endpoint prior to discontinuation from the study.

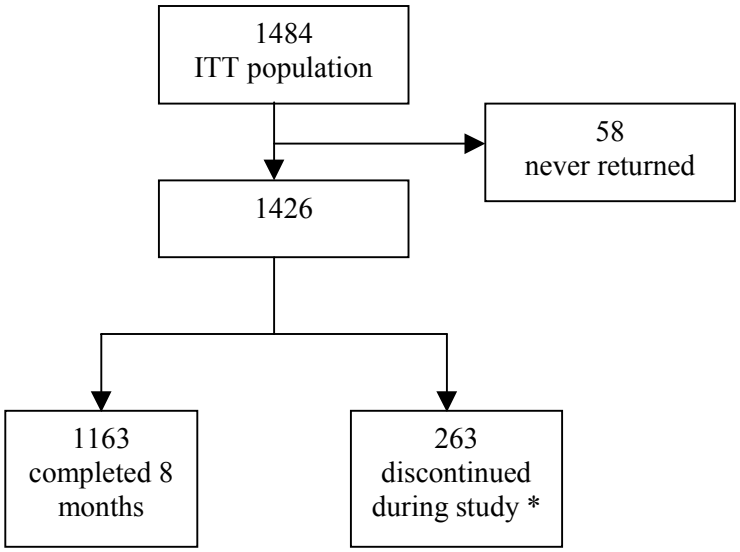
Table 9. Summary of Missing Data for Primary Endpoint (ITT Population)

	Placebo (N=741)	Valtrex (N=743)	Total (N=1484)
Susceptible partner discontinuations *, n	163 (22%)	158 (21%)	321 (22%)
Length of time followed for primary endpoint prior to study discontinuation			
0 - <3 months	90 (55%)	85 (54%)	175 (55%)
3 - <6 months	55 (34%)	52 (33%)	107 (33%)
>6 months	18 (11%)	21 (13%)	39 (12%)

* one subject in placebo group who discontinued study following primary endpoint not included

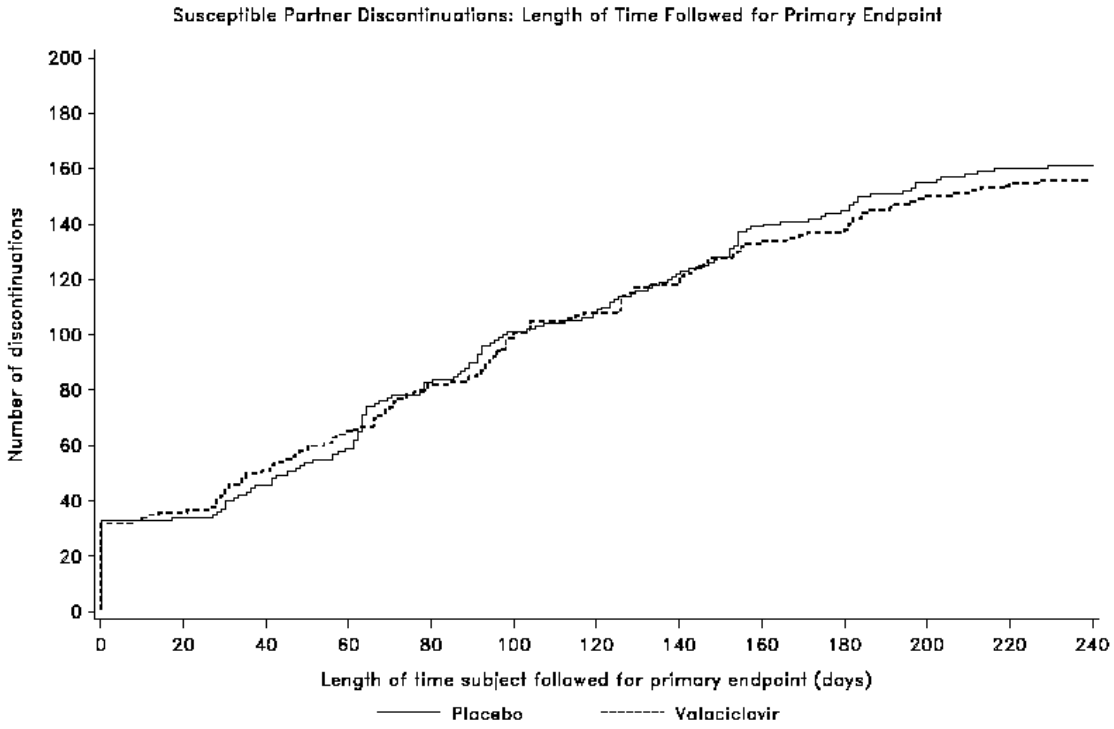
Frequency of susceptible partner discontinuations was similar between the two treatment groups (22% on placebo, 21% on Valtrex), as was the length of time during which patients were followed for the primary endpoint prior to discontinuation. Overall, 146 of 321 (45%) discontinued subjects were followed for the primary endpoint for at least 3 months before discontinuing the study. There were 65 susceptible partners with a zero length of time followed for the primary endpoint; these 65 subjects were divided equally between Valtrex and placebo groups: 58 susceptible partners discontinued the study with no post-treatment follow-up data for the primary endpoint and a further 7 susceptible partners had positive or atypical HSV-2 serology at randomization. Figure 4 provides a visual depiction of disposition of the ITT population. Figure 5 illustrates that the pattern of discontinuations over time for the placebo and Valtrex groups was very similar, providing evidence that discontinuation occurred independently of treatment.

Figure 4. Disposition of the ITT population



* Includes 7 susceptible partners with positive or atypical HSV-2 serology at randomization

Figure 5. Susceptible Partner Discontinuations: Length of Time Followed for Primary Endpoint



The primary analysis compared the proportion of couples with clinical evidence of a first episode of genital HSV-2 in the susceptible partner. In this analysis, couples with missing data are included as not having transmitted. This method accords with a "last-value-carried forward" approach and with the assumption that susceptible partners who developed symptoms would present to the clinic.

The potential sensitivity of the above analysis to different approaches to handling missing data was thoroughly explored in consultation with external experts. The following analysis approaches were used to evaluate the impact of missing data on the primary endpoint.

a) Excluding missing data -- susceptible partner discontinuations were excluded from the analysis.
b) Event imputation -- Events for couples with missing data were imputed at the placebo rate for both treatment groups. Excluding susceptible partner discontinuations, the placebo event rate was 2.8% (16/578). Since this translates as 4.4 events for Valtrex and an integer number of events is required for the analysis, analysis was performed firstly adding 4 events to placebo and Valtrex treatment groups and secondly adding 5 events to both groups.
c) Score penalty for missing data -- In this analysis, all subjects with the event were given a score of 1, subjects completing the study with no event a score of 0 and those with missing data a score of the placebo rate (excluding discontinuations = 0.028). Analysis was performed using the extended Mantel-Haenszel test.
d) Time-to-event analysis -- Time to event analysis explicitly allows for differential length of follow-up. In this analysis, couples with no evidence of a first episode of symptomatic HSV-2 infection were included as censored at their last time point when they were confirmed not to have symptomatic HSV-2 infection. In addition to the discontinuations, there were 20 susceptible partners who were positive/atypical for HSV-2 at baseline; these subjects were censored at time zero in this analysis.

Results of these analyses are provided below in Table 10.

Table 10. Summary of Sensitivity Analyses for Primary Endpoint (ITT Population)

Analysis	Point Estimate	95% confidence limit	p-value
Primary	Odds Ratio = 0.24	(0.06, 0.76)	0.011
Excluding discontinuations	Odds Ratio = 0.25	(0.06, 0.77)	0.012
Placebo rate imputed for discontinuations: 4 events added 5 events added	 Odds Ratio = 0.39 Odds Ratio = 0.42	 (0.15, 0.94) (0.17, 0.96)	 0.033 0.040
Score penalty for missing data	Not applicable	Not applicable	0.005
Time-to-event*	Hazard Ratio = 0.25	(0.08, 0.75)	0.008

* log rank test allowing for strata

An analysis including all discontinuations as treatment failures was not performed as this approach is not appropriate for a transmission trial with a low incidence of endpoints. An analysis which includes discontinuations as transmissions would be dominated by a comparison of discontinuations; frequency of discontinuation and time to discontinuation were similar between treatments. A study designed to detect a difference under these assumptions would be impossible to conduct.

In addition to the analysis performed above, an investigation was conducted to investigate what changes in the number of primary endpoints would result in a non-significant p-value. Results are shown in Table 11.

Table 11. Summary of Effect of Changes in Number of Primary Endpoints

	Primary Endpoints				
	Placebo	Valtrex	Odds Ratio	95% CI	P-value*
Original Analysis	16	4	0.24	0.06, 0.76	0.011
Removing 1 Placebo	15	4	0.26	0.06, 0.83	0.018
Removing 2 Placebo	14	4	0.28	0.07, 0.90	0.029
Removing 3 Placebo	13	4	0.30	0.07, 0.99	0.047
Removing 4 Placebo	12	4	0.33	0.08,1.09	0.074
Removing 1 Valtrex	16	3	0.18	0.03, 0.65	0.004
Removing 2 Valtrex	16	2	0.12	0.01, 0.52	0.001
Removing 1 Valtrex, 1 Placebo	15	3	0.20	0.04, 0.70	0.007
Removing 1 Valtrex, 2 Placebo	14	3	0.21	0.04, 0.76	0.012
Removing 1 Valtrex, 3 Placebo	13	3	0.23	0.04, 0.83	0.020
Adding 1 Valtrex	16	5	0.31	0.09, 0.88	0.025
Adding 2 Valtrex	16	6	0.37	0.12, 1.00	0.0498

* results may vary slightly depending on strata of the discounted endpoint

Removal of up to 3 placebo endpoints maintains a statistically significant result at $p<0.05$.

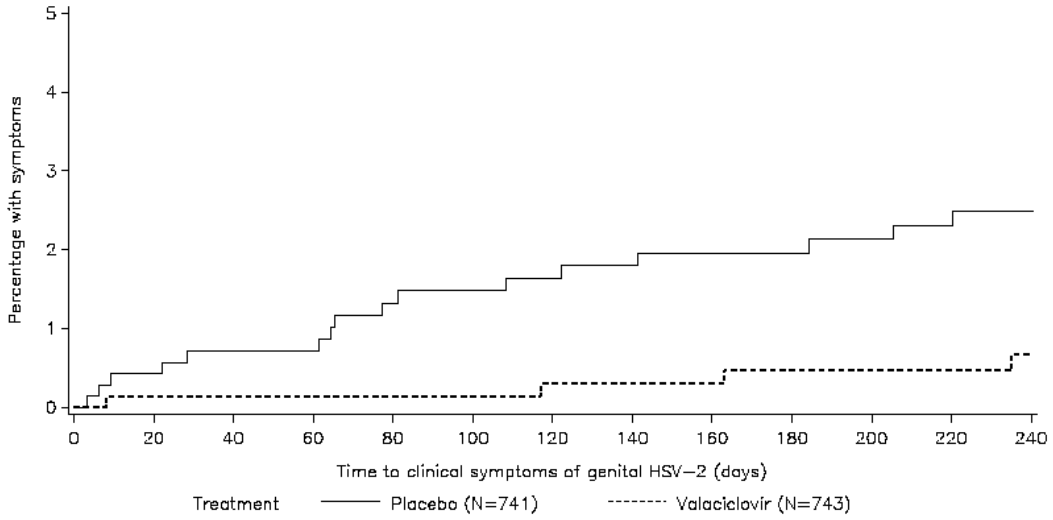
This set of sensitivity analyses demonstrated that the primary analysis (which categorized patients with missing data as non-transmission cases) was robust in the face of reasonable assumptions regarding missing data. Of these analyses, the most intuitively appealing is the sensitivity analysis where missing endpoints in both treatment groups are imputed at the overall placebo rate. The result of this sensitivity analysis is consistent with the primary analysis of the study and provides further support for superiority of Valtrex over placebo.

4.8. Secondary efficacy results

4.8.1. Time to clinical symptoms of genital HSV-2 infection in susceptible partners

Time to clinical symptoms was significantly shorter in the placebo group compared to the Valtrex group (HR = 0.25 [95% CI: 0.08, 0.75]; p = 0.008) with a difference in estimated proportions at 8 months of 1.8% (95% CI: 0.4% to 3.2%) (see Figure 6). The estimated proportions of susceptible partners with no clinical symptoms at 8 months were 97.5% in the placebo group and 99.3% in the Valtrex group.

Figure 6. Kaplan-Meier Estimates of Time to Clinical Symptoms of Genital HSV-2 in Susceptible Partners



4.8.2. Overall acquisition of genital HSV-2 infection in susceptible partners

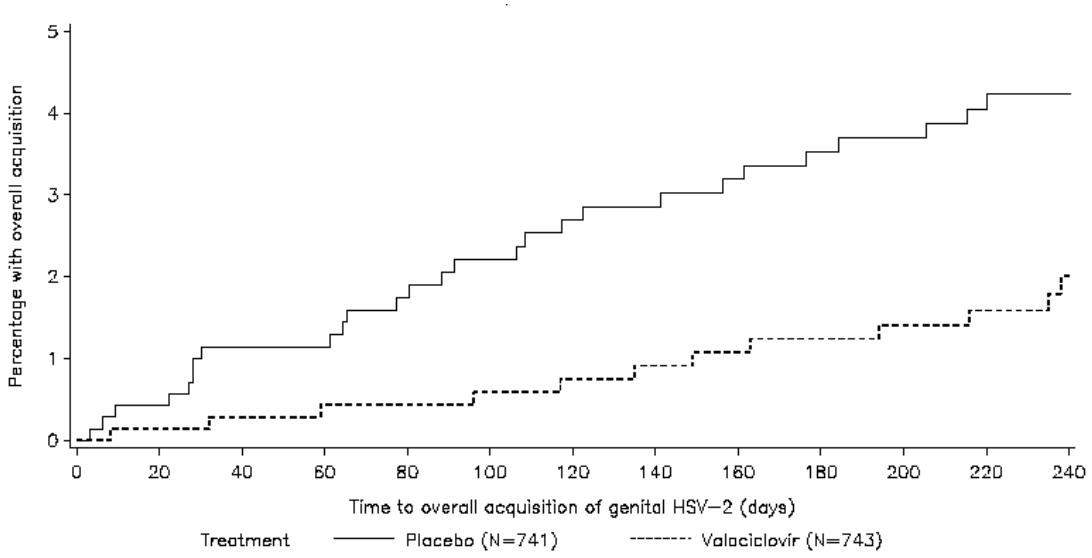
The proportion of couples with overall acquisition of genital HSV-2 infection (i.e., symptomatic genital herpes as defined for the primary endpoint and/or HSV-2 seroconversion) in the susceptible partner was 3.6% (27/741) in the placebo group and 1.9% (14/743) in the Valtrex group [p=0.054, odds ratio: 0.50 (0.24, 1.01), approximate relative risk (95% CI): 0.52, (0.27, 0.97)], i.e., a reduction of 48%. The overall acquisition of genital HSV-2 in susceptible partners is summarized in Table 12 below.

Table 12. Summary of Overall Acquisition of Genital HSV-2 Infection in Susceptible Partners (ITT Population)

	Placebo (N = 741)	Valtrex (N = 743)
Number of Overall Acquisitions, n	27 (3.6%)	14 (1.9%)
Odds Ratio (95% CI)		0.50 (0.24,1.01)
p-value		0.054
Approx. Relative Risk (95% CI)		0.52 (0.27, 0.97)

Time to overall acquisition was significantly shorter in the placebo group compared to the Valtrex group (HR = 0.52 [95% CI: 0.27, 0.99]; p=0.039) with a difference in estimated proportions at 8 months of 2.2% (95% CI: 0.3% to 4.2%) (see Figure 7). The estimated proportions of susceptible partners with no overall acquisition at 8 months were 95.8% in the placebo group and 98.0% in the Valtrex group.

Figure 7. Kaplan-Meier Estimates of Time to Overall Acquisition of Genital HSV-2 in Susceptible Partners



4.8.3. HSV-2 seroconversion in susceptible partners

As a subset of the overall acquisition population, HSV-2 seroconversion was also measured in the interest of completeness. The proportion of couples with HSV-2 seroconversion in the susceptible partner was 3.2% (24/741) in the placebo group and 1.6% (12/743) in the Valtrex group (p=0.060) and is summarized in Table 13 below. In addition, the comparison between treatment groups for time to HSV-2 seroconversion showed a difference in estimated proportions at 8 months of 1.7% (95% CI: -0.1%, 3.5%) (p=0.069). The estimated proportions of susceptible partners who had not seroconverted by 8 months were 96.6% in the placebo group and 98.3% in the Valtrex group.

Table 13. Summary of HSV-2 Seroconversion in Susceptible Partners (ITT Population)

	Placebo (N = 741)	Valtrex (N = 743)
Number of HSV-2 Seroconversions, n	24 (3.2%)	12 (1.6%)
Odds Ratio (95% CI)		0.49 (0.22, 1.03)
p-value		0.060
Approximate Relative Risk (95% CI)		0.50 (0.25, 0.99)

4.8.4. Asymptomatic HSV-2 seroconversion in susceptible partners

As a subset of the overall acquisition population, asymptomatic HSV-2 seroconversion was also measured in the interest of completeness. The proportion of couples with asymptomatic seroconversion in the susceptible partner was 1.5% (11/741) in the placebo group and 1.3% (10/743) in the Valtrex (p=0.996). Time to asymptomatic

seroconversion was not significantly different in the placebo group compared to the Valtrex group (p=0.804) with a difference in estimated proportions at 8 months of 0.5% (95% CI: -1.0%, 1.9%). The estimated proportions of susceptible partners with no asymptomatic seroconversion at 8 months were 98.2% in the placebo group and 98.6% in the Valtrex group.

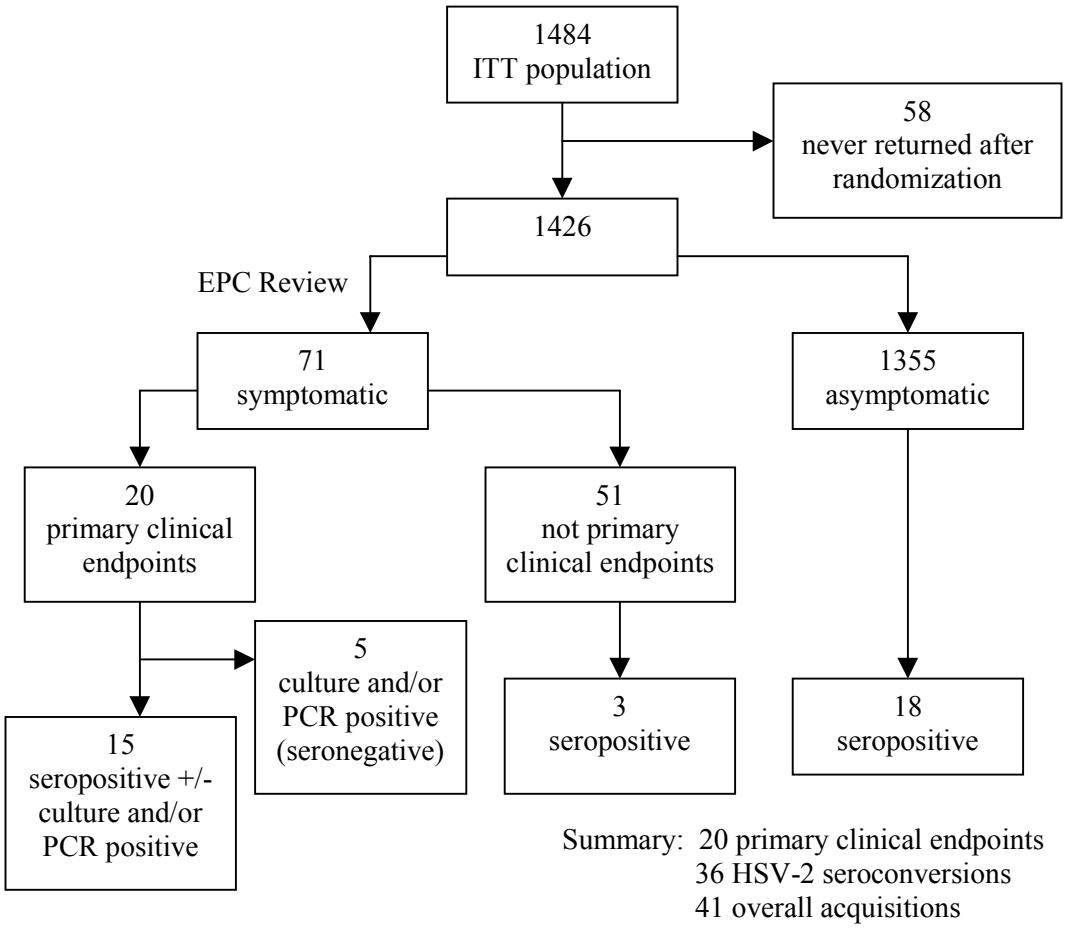
A summary of asymptomatic HSV-2 seroconversion in susceptible partners is presented below in Table 14.

Table 14. Summary of Asymptomatic HSV-2 Seroconversion in Susceptible Partners (ITT Population)

	Placebo (N = 741)	Valtrex (N = 743)
Number of Asymptomatic Seroconversions, n	11 (1.5%)	10 (1.3%)
Odds Ratio (95% CI)		0.91 (0.34, 2.37)
p-value		0.996
Approx. Relative Risk (95% CI)		0.91 (0.39, 2.12)

A flow chart providing an overall summary of the endpoint evaluation for clinical genital HSV-2 disease or HSV-2 infection in susceptible partners is provided in Figure 8.

Figure 8. Overall Summary of Endpoint Evaluation in Susceptible Partners



4.8.5. Clinical evidence of HSV-1 infection in susceptible partners

There were no susceptible partners with clinical evidence of a first episode of genital HSV-1 infection in either treatment group.

However, 4 HSV-1 seroconversions occurred in susceptible partners in the placebo group without signs/symptoms of genital herpes; no HSV-1 seroconversions were observed in susceptible partners in the Valtrex group. Each of these susceptible partners was HSV-1 seronegative at randomization and seroconverted to HSV-1 during the course of participating in the study. Of these 4 susceptible partners, two had source partners who were HSV-1 seropositive at screen while the other two had source partners who were HSV-1 seronegative at screen. As there were no additional HSV-1 serology data collected on source partners after the initial screen sample, it is not possible to make a conclusive statement about the circumstances of these seroconversions.

4.8.6. Time to first recurrence of genital HSV-2 in source partners

More placebo-treated source partners had genital HSV-2 recurrences than Valtrex-treated source partners (placebo: 573/741, 77%; Valtrex: 288/743, 39%). Time to first recurrence of genital HSV-2 in the source partner was significantly shorter in the placebo group compared to the Valtrex group ($p<0.001$) with a difference in estimated proportions at 8 months of 39% (95% CI: 34%, 44%).

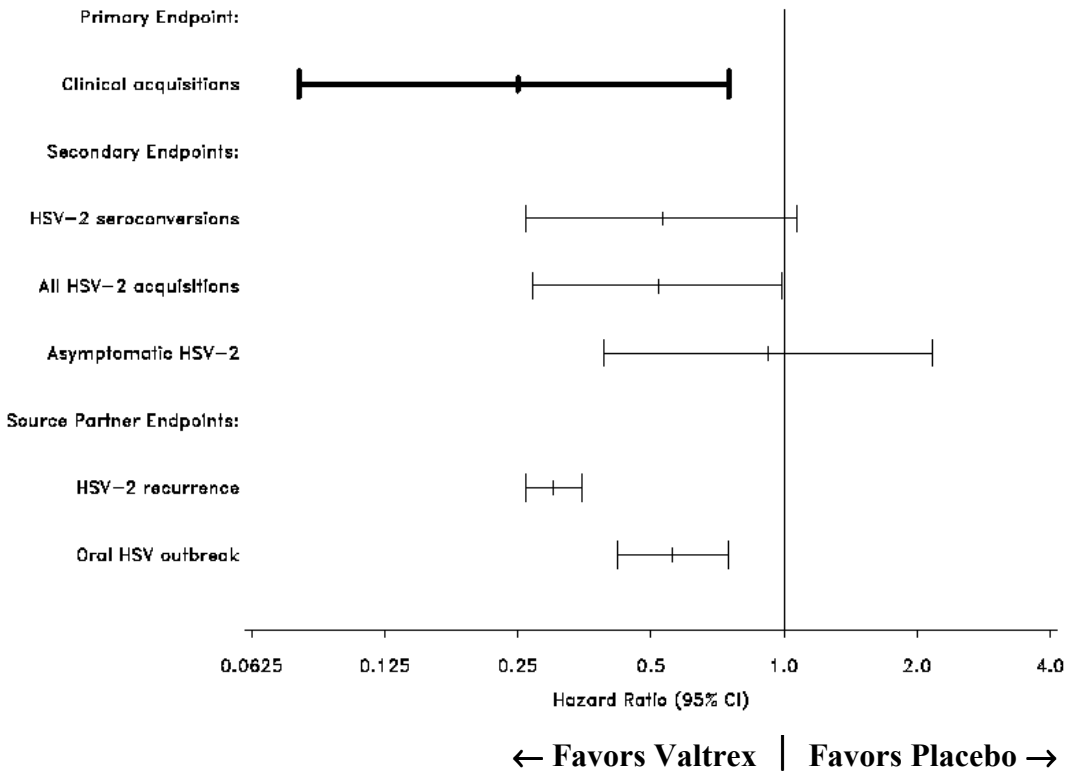
4.8.7. Time to first oral HSV outbreak in source partners

More placebo-treated source partners reported oral HSV outbreaks than Valtrex-treated source partners (placebo: 120/719, 17%; Valtrex 71/715, 10%). Time to first oral HSV outbreak in the source partner was significantly shorter in the placebo group compared to the Valtrex group ($p<0.001$) with a difference in estimated proportions at 8 months of 7% (95% CI: 3%, 11%).

4.8.8. Summary of hazard ratios for time-to-event endpoints

Figure 9 summarizes the hazard ratios (Valtrex/placebo) and associated 95% CIs for the time-to-event analyses. The weight of evidence across these endpoints points to a consistent effect of Valtrex.

Figure 9. Hazard Ratios (95% CI) for Multiple Endpoints Across Treatment



4.9. Additional analyses

The impact of factors potentially important in the transmission of HSV-2 infection is examined in this section. Section 4.9.1 presents results by subgroups and explores the evidence that the efficacy of Valtrex varies in these categories through interaction tests. Section 4.9.2 includes the results of a pre-specified covariate analysis, which investigates the extent to which specific factors influence transmission of HSV-2 after allowing for effects produced by the other factors.

4.9.1. Subgroup analyses

Based on previously published data regarding factors that potentially influence HSV-2 transmission or acquisition, various subgroups of the study population were identified for further analysis to determine whether there is evidence that Valtrex efficacy varies among these subgroups. A summary by subgroup of clinical evidence of first episode of genital HSV-2 in susceptible partners is provided in Table 15 and of overall acquisition of genital HSV-2 infection in susceptible partners in Table 16.

Table 15. Summary of Clinical Evidence of First Episode of Genital HSV-2 in Susceptible Partners by Subgroup

	Placebo (N=741)	Valtrex (N=743)
Overall	16/741 (2.2%)	4/743 (0.5%)
Gender of susceptible partner:		
Female	10/244 (4.1%)	2/244 (0.8%)
Male	6/497 (1.2%)	2/499 (0.4%)
HSV-1 status of susceptible partner:		
HSV-1 positive/atypical	11/514 (2.1%)	2/517 (0.4%)
HSV-1 negative	5/227 (2.2%)	2/226 (0.9%)
Race of susceptible partner		
White	14 / 666 (2.1%)	4/664 (0.6%)
Other races	2 / 75 (2.7%)	0 / 79
Condom use during study*		
Never	11/389 (2.8%)	4/401 (1.0%)
Sometimes (1-90%)	2/102 (2.0%)	0/91 (0.0%)
Nearly Always (>90%)	3/212 (1.4%)	0/211 (0.0%)
Sexual Contacts per month		
≤5	3/257 (1.2%)	1/225 (0.4%)
>5-10	4/261 (1.5%)	0/310 (0.0%)
>10	9/191 (4.7%)	3/176 (1.7%)
Age of susceptible partner		
<35	12/374 (3.2%)	1 / 351 (0.3%)
≥35	4/367 (1.1%)	3 /392 (0.8%)
Country		
US	11/395 (2.8%)	4/408 (1.0%)
Non-US	5/346 (1.4%)	0 / 335
Time since first episode to study start (source partner):		
< 7 years	9 / 380 (2.4%)	2 / 351 (0.6%)
≧ 7 years	7 / 359 (1.9%)	2 / 389 (0.5%)

* Median usage over months 1-8

Table 16. Summary of Overall Acquisition of Genital HSV-2 Infection in Susceptible Partners by Subgroup

	Placebo (N=741)	Valtrex (N=743)
Overall	27/741 (3.6%)	14/743 (1.9%)
Gender of susceptible partner:		
Female	18/244 (7.4%)	8/244 (3.3%)
Male	9/497 (1.8%)	6/499 (1.2%)
HSV-1 status of susceptible partner:		
HSV-1 positive/atypical	19/514 (3.7%)	10/517 (1.9%)
HSV-1 negative	8/227 (3.5%)	4/226 (1.8%)
Race of susceptible partner		
White	25 / 666 (3.8%)	12 / 664 (1.8%)
Other races	2 / 75 (2.7%)	2 / 79 (2.5%)
Condom use during study*		
Never	16/389 (4.1%)	7/401 (1.7%)
Sometimes (1-90%)	4/102 (3.9%)	3/91 (3.3%)
Nearly Always (>90%)	7/212 (3.3%)	4/211 (1.9%)
Sexual Contacts per month		
≤5	6/257 (2.3%)	1/225 (0.4%)
>5-10	8/261 (3.1%)	6/310 (1.9%)
>10	13/191 (6.8%)	7/176 (4.0%)
Age of susceptible partner		
<35	17/374 (4.5%)	6/351 (1.7%)
≥35	10/367 (2.7%)	8/392 (2.0%)
Country		
US	12/395 (3.0%)	10/408 (2.5%)
Non-US	15/346 (4.3%)	4/335 (1.2%)
Time since first episode to study start (source partner):		
< 7 years	16 / 380 (4.2%)	9 / 351 (2.6%)
≧ 7 years	11 / 359 (3.1%)	5 / 389 (1.3%)

* Median usage over months 1-8

The data in Tables 15 and 16 were examined to assess whether the effect of Valtrex varied across the subgroups defined above (e.g., is there any evidence that Valtrex was more effective in preventing male-to-female transmissions compared to female-to-male transmissions?). This evaluation was done statistically using interaction tests. Results are shown in Table 17.

There were more male to female transmissions of symptomatic genital herpes than female to male transmissions (12 female and 8 male clinical acquisitions; 26 female and 15 male overall acquisitions of genital HSV-2). The study was not designed and not adequately powered to independently demonstrate treatment benefit in males and females but differences in favor of Valtrex were observed in both subgroups. A treatment by gender interaction test for the primary endpoint showed that the study provides no evidence of an

effect of gender on the efficacy of Valtrex in reducing the transmission of symptomatic genital herpes (p=1.00).

Numerical differences in favor of Valtrex were observed at all levels of condom use. Specifically, for the stratum for condom use 'nearly always', there were 3 clinical, symptomatic acquisitions in the placebo group and none in the Valtrex group. For the 'sometimes' category, there were 2 cases in the placebo group and 0 in the Valtrex group and for the 'never' category, there were 11 cases in the placebo group and 4 in the Valtrex group. The treatment by condom use interaction test was not significant (p=0.53 for 'never' vs other use, p=1.00 for 'nearly always' vs other use). Therefore, there is no evidence that the efficacy of Valtrex varied according to condom use.

For the other subgroups identified (HSV-1 positive/negative; white/other races; number of sexual contacts per month; age of susceptible partner; country; time since first HSV-2 episode), there was also no evidence of a difference in Valtrex efficacy across any subgroup. In summary, there was no statistical evidence that the efficacy of Valtrex varied across any of the subgroups tested. Note that because of the small numbers of events, the statistical power of the interaction test to detect a difference in efficacy is limited.

Table 17. Summary of Interaction Tests for Differential Effects Across Subgroups

Interaction	Clinical Evidence of First Episode of Genital HSV-2 p-value	Overall Acquisition of Genital HSV-2 Infection p-value
Treatment by Gender of susceptible partner	1.000	0.730
Treatment by HSV-1 Status (susceptible)	0.584	1.000
Treatment by Race of susceptible partner (White vs other)	1.000	0.600
Treatment by Condom use Never vs other use Nearly always vs other use	 0.530 1.000	 0.523 1.000
Treatment by Sexual contacts ≤5 per month vs rest >10 per month vs rest	 0.560 0.605	 0.410 1.000
Treatment by Age of Susceptible partner <35 vs ≥35	0.122	0.334
Treatment by Country US vs. non-US	0.530	0.182
Treatment by Time since first episode to study start (source partner): < 7 vs ≧ 7 years	1.000	0.737

4.9.2. Covariate analyses

Covariate analysis was performed for the primary endpoint of clinical HSV-2 transmissions and for the secondary endpoint of overall HSV-2 acquisitions. This analysis was conducted to explore what factors may contribute to the risk of transmission of HSV-2.

The study was stratified by gender and susceptible partner's screening HSV-1 serostatus. All models included these stratification factors as well as treatment. Due to their possible influence on HSV-2 transmission, other covariates evaluated were condom use, frequency of sexual contacts, age of susceptible partner, country, and duration of genital herpes. These covariates are the same as those identified as potentially important subgroups in Section 4.9.1, with the exception of race of susceptible partner, which was included in the subgroup analysis but not in the covariate analysis since there were too few transmission events in non-white susceptible partners to allow an appropriate analysis.

Analysis was performed for both proportions of subjects with the event and for time-to-event. Analysis of proportions was performed using logistic regression analysis; time-to-event analysis was performed using Cox's proportional hazards model.

Results of the logistic regression analysis and the proportional hazards analysis were very similar. Tables 18 and 19 show results of the proportional hazards analysis of clinical evidence of first episode of genital HSV-2 and overall acquisition of genital HSV-2 infection in susceptible partners, respectively.

Table 18. Summary of Covariate Analysis for Clinical Evidence of First Episode of Genital HSV-2

	Clinical Evidence of First Episode of Genital HSV-2		
Covariate	**Hazard ratio**	**95% CI**	**P value**
Valtrex / Placebo	0.26	0.09,0.77	0.015
Gender (susceptible): Female / Male	3.10	1.24,7.72	0.015
HSV-1 (susceptible) Negative/positive	1.36	0.52,3.53	0.533
Condom use during study*	0.54	0.28,1.03	0.063
Sexual contacts during study**	2.04	1.10,3.78	0.024
Age (susceptible) ≥35 / < 35 yr	0.53	0.19,1.47	0.225
Country Non-US / US	0.37	0.13,1.04	0.060
Duration of HSV-2 (source): ≥7 / < 7 yr	0.70	0.26,1.86	0.474

* categorized as never; sometimes, nearly always; hazard ratio represents decrease to next category

** categorized as ≤5, >5-10, >10 per month; hazard ratio represents increase to next category

Table 19. Summary of Covariate Analysis Overall Acquisition of Genital HSV-2 Infection

	Overall Acquisition of Genital HSV-2 Infection		
Covariate	**Hazard ratio**	**95% CI**	**P value**
Valtrex / Placebo	0.52	0.27,1.00	0.049
Gender (susceptible): Female / Male	3.66	1.90,7.05	<0.001
HSV-1 (susceptible) Negative/positive	1.41	0.69,2.87	0.342
Condom use during study*	0.85	0.59,1.24	0.410
Sexual contacts during study**	1.87	1.22,2.85	0.004
Age (susceptible) ≥35 / < 35 yr	1.11	0.55,2.23	0.768
Country Non-US / US	0.93	0.48,1.79	0.829
Duration of HSV-2 (source): ≥7 / < 7 yr	0.59	0.29,1.19	0.138

* categorized as never; sometimes, nearly always; hazard ratio represents decrease to next category
** categorized as ≤5, >5-10, >10 per month; hazard ratio represents increase to next category

The magnitude of effect is measured using a hazard ratio (HR), which represents an estimate of relative risk of transmission of HSV-2 at any particular time during the study; a HR >1.0 reflects an increased risk of transmission. For the primary endpoint of clinical evidence of a first episode of genital HSV-2, there was evidence that male-to-female transmissions were more likely than female-to-male transmissions (p=0.015). At any time, the risk of transmission was estimated as 3 times higher for male-to-female compared to female-to-male transmission (HR = 3.10; 95% CI: 1.24, 7.72). Similar results were seen for overall acquisition of genital HSV-2.

For both clinical evidence of a first episode of genital HSV-2 and overall acquisition of genital HSV-2, there was evidence that increasing number of sexual contacts increased the risk of transmission (HR = 2.04; 95% CI: 1.10, 3.78 for clinical disease and HR = 1.87; 95% CI: 1.22, 2.85 for overall acquisition). This finding is not unexpected given that exposure to virus would be expected to be highly correlated with number of contacts. There was some evidence that residing outside of the US (compared to within the US) decreased the risk of transmission of clinical disease (HR = 0.37; 95% CI: 0.13, 1.04), although this was not the case for overall acquisition of infection (HR = 0.93; 95% CI: 0.48, 1.79).

For condom use, there was some evidence that increased use of condoms reduced the risk of symptomatic acquisition (p = 0.063). At any time, the risk of transmission was estimated to be reduced by 46% for subjects 'sometimes' using condoms compared to those 'never' using condoms and by a further 46% for subjects 'nearly always' using condoms compared to those who 'sometimes' used them (HR = 0.54; 95% CI: 0.28,

1.03). For overall acquisition, however, the evidence of a beneficial effect of condom use was less clear (hazard ratio = 0.85; 95% CI: 0.59, 1.24).

After allowing for effects produced by the other covariates, there was no evidence that HSV-2 serological status, age of susceptible partner, or duration of HSV-2 infection in the source partner contributed to the risk of HSV-2 transmission.

4.10. Viral shedding substudy results

4.10.1. Patient demographics and baseline characteristics

A total of 89 subjects (50 placebo, 39 Valtrex) from 3 sites in the US were included in the asymptomatic shedding substudy. A total of 85 (96%) subjects completed the substudy. Three subjects (3%) withdrew their consent, and one subject (1%) listed 'other' as the reason for premature discontinuation. The majority of the subjects who participated in the substudy were female (68/89, 76%) and white (80/89, 90%). The HSV serology status of the substudy participants was evenly distributed between the two treatment groups, with 30/50 (60%) in the placebo group and 23/39 (59%) in the Valtrex group being HSV-1 negative.

4.10.2. Shedding results

The substudy was designed to assess the efficacy of Valtrex 500mg once daily compared with placebo in the suppression of asymptomatic shedding over a 2-month period (approximately 60 days). The median number of days participants spent in the substudy was 58.0 days for subjects in each treatment group. In the placebo group, 49/50 (98%) subjects remained in the study for at least 40 days and in the Valtrex group 37/39 (95%) subjects remained in the study for at least 40 days. Overall shedding results are summarized in Table 20.

Table 20. Total and Asymptomatic HSV Shedding

	Placebo (N=50)	Valtrex (N=39)	p-value
Total Shedding			
Rate, mean % days	10.8%	2.9%	p<0.001
Shedding on at least one day, n	41 (82%)	19 (49%)	p=0.002
HSV DNA copies/mL on all days (mean log10)	4.2	1.7	p<0.001
HSV DNA copies/mL on shedding days (mean log10)	n=41 5.1	n=19 3.5	p<0.001
Asymptomatic Shedding			
Rate, mean % days	7.8%	2.8%	p<0.001
Asymptomatic shedding on at least one day, n	36 (72%)	19 (49%)	p=0.040
HSV DNA copies/mL on asymptomatic shedding days (mean log 10)	n=36 4.4	n=19 3.4	p=0.009

Valtrex was associated with significant reductions in both the number of days on which virus was shed, and the quantity of virus shed. The mean proportion of days on which patients shed virus (total shedding rate) was reduced from 10.8% in the placebo group to 2.9% in the Valtrex group ($p<0.001$); a significant reduction was also seen in the mean asymptomatic shedding rate (i.e., on days when lesions were not present). There was a 1.6 $\log_{10}$ (approximately 40-fold) reduction in quantity of HSV-2 shedding (HSV DNA copies/mL) on shedding days in the Valtrex recipients compared with placebo recipients ($p<0.001$) and a 10-fold reduction on asymptomatic shedding days ($p=0.009$). Relative to placebo, Valtrex showed a 40% relative reduction in the proportion of patients with shedding (symptomatic or asymptomatic) on at least one day and a 32% relative reduction in the proportion of patients with asymptomatic shedding on at least one day.

5. STUDY HS2AB3009: SAFETY

5.1. Extent of Exposure

During the double-blind phase of study HS2AB3009, 1364 (92%) source partners were considered compliant in taking study medication; 673 (91%) in the placebo group and 691 (93%) in the Valtrex group. Non-compliance was defined as failure to take medication for at least 80% of the time on double-blind medication.

During the double-blind phase of the study, 743 source partners were exposed to Valtrex 500mg once daily therapy. The treatment stop date for 44 subjects on placebo and 47 subjects on Valtrex was unknown; therefore the number of days on double-blind suppressive therapy was assessed for 1393 of the 1484 source partners exposed to study medication. The median number of days on which source partners received double-blind suppressive therapy was 231 in the placebo group and 240 in the Valtrex group. The study duration was 8 months, however, not all source partners took the double-blind therapy as prescribed (Valtrex 500mg once daily or placebo) and/or the monthly clinic visit schedule was not explicitly followed.

The protocol stipulated a 5-day treatment course with open-label Valtrex for recurrences of genital herpes. Six hundred eighty-eight (688) source partners were exposed to Valtrex for open-label treatment of HSV recurrences. For nine of these subjects, the treatment stop date was unknown; therefore, the number of days on open-label Valtrex therapy could not be determined. The median number of days on open-label Valtrex was 10. The source partner (randomized to placebo) with the maximum exposure to Valtrex open-label therapy experienced 18 recurrences during the study.

Forty-two susceptible partners were exposed to Valtrex study medication for open-label treatment of suspected first episodes HSV. The median number of days on open-label Valtrex was 10. In addition, two susceptible partners received commercial Valtrex**;** therefore a total of 44 susceptible partners were exposed to Valtrex**.**

5.2. Adverse Events

A total of 553/741 (75%) placebo source partners and 588/743 (79%) Valtrex source partners experienced an adverse event during the double-blind phase of the study. Frequently reported AEs (≥5% incidence) in any treatment group regardless of causal relationship to study drug are shown in Table 21 below.

Table 21. Summary of Frequently Reported (≥5%) Adverse Events in Source Partners During Double-Blind Phase (ITT Population)

Adverse Event	Placebo N=741 n	Valtrex N=743 n
ANY EVENT	553 (75%)	588 (79%)
Headache NOS*	192 (26%)	215 (29%)
Nasopharyngitis	110 (15%)	122 (16%)
Upper respiratory tract infection NOS*	75 (10%)	69 (9%)
Pharyngolaryngeal pain	55 (7%)	61 (8%)
Diarrhea NOS*	50 (7%)	62 (8%)
Influenza	51 (7%)	60 (8%)
Nausea	48 (6%)	59 (8%)
Back pain	44 (6%)	62 (8%)
Sinusitis NOS*	34 (5%)	56 (8%)
Abdominal pain upper	35 (5%)	38 (5%)

* NOS = Not otherwise specified

During the double-blind phase of the study, the incidences of AEs in source partners were similar across treatment groups. Headache was the most frequently reported adverse event among the source partners (reported by 26% of placebo subjects and 29% of Valtrex subjects).

Eleven (25%) of 44 susceptible partners (including two who received commercial Valtrex that were excluded from study-drug exposure calculations) treated with open-label Valtrex episodic therapy for a suspected first clinical episode reported an adverse event. Infections and infestations was the body system with the highest incidence of adverse events (4/44; 9%) followed by the gastrointestinal disorders body system which had an incidence rate of 7% (3/44). The individual events reported and the number of subjects reporting each event are summarized in Table 22 below.

Table 22. Summary of Adverse Events in Susceptible Partners Treated with Open-Label Valtrex

Adverse Event	Valtrex N=44 n
ANY EVENT	11 (25%)
Flatulence	2 (5%)
Loose stools	2 (5%)
Aphthous stomatis	1 (2%)
Fatigue	1 (2%)
Fungal infection NOS*	1 (2%)
Urinary tract infection NOS*	1 (2%)
Vaginal candidiasis	1 (2%)
Vaginosis fungal NOS*	1 (2%)
Lumbar vertebral fracture	1 (2%)
Headache NOS*	1 (2%)
Difficulty in micturition	1 (2%)
Cough	1 (2%)
Pharyngolaryngeal pain	1 (2%)
Rhinorrhea	1 (2%)

* NOS=Not Otherwise Specified

5.3. Drug-Related Adverse Events

Sixty-seven (9%) placebo source partners compared to 84 (11%) Valtrex source partners experienced a drug-related adverse event during the double-blind suppressive phase of the study. The most frequently reported drug-related events were headache and nausea in both treatment groups. During the open-label treatment phase, 16 (1%) source partners experienced a drug-related adverse event.

Only 2 (5%) of 44 susceptible partners reported a drug-related adverse event (flatulence and loose stools) while being treated with open-label therapy for a suspected first episode of genital HSV.

5.4. Serious Adverse Events

5.4.1. Double-blind phase

Twenty-six source partners, 12 (2%) of 741 receiving placebo and 14 (2%) of 743 receiving Valtrex, experienced a serious adverse event (SAE) during the double-blind phase of the study. The individual subjects and associated SAEs are listed in Table 23 below.

Table 23. Summary of Serious Adverse Events Reported by Source Partners in Double-Blind Phase of Study HS2AB3009

Subject	Treatment	Serious Adverse Event	Withdrawn from Study
3008	Placebo	Pancreatitis NOS*	No
3912	Placebo	Lower limb fracture NOS*, hand fracture	No
3998	Placebo	Erysipelas	No
9980	Placebo	Abortion spontaneous NOS*	No
11578	Placebo	Appendicitis	No
12170	Placebo	Abortion spontaneous NOS*	No
16642	Placebo	Coronary artery disease NOS*	Yes
17092	Placebo	Intervertebral disc herniation	No
18282	Placebo	Abortion spontaneous NOS*	No
18634	Placebo	Anal canal cancer NOS*	No
20694	Placebo	Bartholin's cyst	No
35980	Placebo	Ovarian cyst	No
3204	Valtrex	Breast cancer NOS*	No
3920	Valtrex	Meningitis NOS*	No
4464	Valtrex	Intervertebral disc herniation	No
8720	Valtrex	Syncope	No
9574	Valtrex	Osteoarthritis NOS*	No
9598	Valtrex	Uterine fibroid	No
9784	Valtrex	Lymphadenitis NOS*	No
11100	Valtrex	Glomerulonephritis NOS*	Yes
11168	Valtrex	Arthralgia	No
11988	Valtrex	Vasovagal attack	No
18612	Valtrex	Localized infection	No
19308	Valtrex	Abortion spontaneous NOS*	No
19534	Valtrex	Appendicitis	No
21822	Valtrex	Intestinal obstruction NOS*	No

*NOS=Not Otherwise Specified

No SAE was judged by the investigator(s) to be associated with study medication. No SAEs were reported for source partners during open-label treatment for HSV recurrences. One SAE was reported (lumbar vertebral fracture) in a susceptible partner during open-label treatment. This SAE was judged by the investigator to not be associated with study medication.

There were no cases of thrombotic microangiopathies (TMA), thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) in this study.

5.4.2. Open-label suppression phase

This section provides new data regarding SAE reporting during the open-label suppression phase of HS2AB3009 that were not previously provided in the Supplemental NDA application.

Twenty of over 900 subjects enrolled in the open label suppression phase of Study HS2AB3009 reported serious adverse events from the beginning of the open label phase through 31 January 2003. The individual subjects and associated SAEs are listed in Table 24 below.

Table 24. Summary of Serious Adverse Events in Study HS2AB3009 Open-Label Phase

Subject	Serious Adverse Event	Withdrawn from Study
3036	Lymphoma NOS*	No
3912	Tinnitus	No
4614	Gastritis NOS*, Hiatus hernia	Yes
4034	Postoperative haematoma	No
4594	Renal cell carcinoma stage unspecified	No
9492	Abortion spontaneous NOS*	No
9560	Breast cancer NOS*	No
10044	Abortion Spontaneous NOS*	No
10980	Inguinal hernia NOS*	No
11300	Asthma NOS*	No
11944	Angina unstable	No
12392	Cholelithiasis	No
12398	Ligament injury NOS*, Meniscus lesion	No
12774	Bile duct stone, Cholelithiasis, Pancreatitis NOS*	No
12946	Bipolar disorder	No
13750	Radius fracture	No
18256	Dermoid cyst of ovary	No
18260	Bipolar I disorder	No
21780	Uterine fibroids	No
21802	Appendicitis	No

*NOS =Not Otherwise Specified

One SAE (gastritis NOS, subject 4614) was judged by the investigator(s) to have a reasonable possibility of being associated with study medication.

There were no cases of TMA, TTP or HUS in the open label phase of this study through 31 January 2003.

5.5. Deaths

There were no deaths in study HS2AB3009.

5.6. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

Five of 741 (<1%) source partners in the placebo group and 12 of 743 (2%) source partners in the Valtrex group experienced an adverse event leading to discontinuation of study drug during the double-blind phase of the study (Table 25).

Table 25. Summary of Adverse Events Leading to Discontinuation of Study Drug in Double-Blind Phase (Source Partner)

Adverse Event	Placebo N=741 n	Valtrex N=743 n
ANY EVENT	5 (<1%)	12 (2%)
Nervous system disorders	2 (<1%)	6 (<1%)
Gastrointestinal disorders	2 (<1%)	5 (<1%)
Renal and urinary disorders	0	2 (<1%)
Skin and subcutaneous tissue disorders	0	2 (<1%)
General disorders and administration site conditions	1 (<1%)	1 (<1%)
Cardiac disorders	1 (<1%)	0
Infections and infestations	0	1 (<1%)
Musculoskeletal and connective tissue disorders	1 (<1%)	0
Psychiatric disorders	1 (<1%)	0
Reproductive system and breast disorders	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders	0	1 (<1%)

None of the AEs resulting in study drug discontinuation in either treatment group was reported in >1% of the study population. Eleven of the 12 Valtrex source partners who experienced an adverse event leading to discontinuation of study drug were also discontinued from the study. However, one subject remained in the study after being taken off study medication due to an AE (urticarial rash).

There were no AEs leading to discontinuation of study drug during the open-label treatment phase of the study for source or susceptible partners.

5.7. Pregnancies

A total of 16 pregnancies were reported during the double-blind phase of the study, 11 of which occurred in source partners and 5 in susceptible partners. There was no evidence of any adverse effect of Valtrex on the outcome of these pregnancies. Of the 16 reported pregnancies, 15 couples discontinued the study (both partners). However, 1 susceptible partner of a pregnant source partner remained in the study. Despite discontinuation from the study, an effort was made to follow all pregnancies to term.

Source Partners

Of the 11 pregnancies which were reported in source partners, 4 occurred in individuals who were randomized to receive Valtrex during the double-blind phase of the study. Two of these pregnancies resulted in a spontaneous abortion (not considered by the investigator to be study drug related), and 2 pregnancies resulted in the delivery of healthy babies.

Seven of the 11 pregnancies in source partners occurred in individuals receiving placebo during the study. Three of these resulted in spontaneous abortions, 1 was an elective termination, and 3 resulted in deliveries of healthy babies.

Susceptible Partners

Of the 5 pregnancies that occurred in susceptible partners, 4 were reported in individuals who did not receive Valtrex treatment during the study. One pregnancy occurred in a susceptible partner who received Valtrex for the treatment of a suspected episode of HSV and who was later confirmed by the endpoint committee to have acquired HSV-2 from her partner. She elected to terminate the pregnancy.

5.8. Laboratory Data

Blood samples for hematology and clinical chemistry evaluation were obtained from source partners at Screen, and at the Month 8 and/or the final study visit. There were no clinically significant differences within treatment groups over time and/or between treatments groups for the proportion of subjects with laboratory values outside the normal range.

The criteria for determining clinically significant laboratory abnormalities in Valtrex studies were recommended *a priori* by the FDA. A summary of clinically significant laboratory abnormalities reported in the study is presented in Table 26 below.

Table 26. Clinically Significant Laboratory Abnormalities in Source Partners (ITT Population)

	Placebo N=741	Valtrex N=743
Alkaline Phosphatase (>1.5 x NRH) [1]	0/740	0/743
ALT (>2 x NRH)	16/739 (2%)	11/742 (1%)
Creatinine (>1.5 x NRH)	0/740	0/743
Hemoglobin (<0.8 x NRL) [2]	3/737 (<1%)	5/736 (<1%)
Platelet Count (<100,000/mm3)	0/732	1/735 (<1%)
White blood cells (<0.75 x NRL)	13/737 (2%)	8/736 (1%)

[1] NRH = high limit of the normal range
[2] NRL = low limit of the normal range

The incidence of clinically significant laboratory abnormalities was similar between the treatment groups.

5.9. Long-term treatment effects

In order to assess any potential long-term treatment effects in Study HS2AB3009, AEs were summarized for two time periods during the study: Months 0 (randomization) through Month 4 and from the end of Month 4 to Month 8. A summary of frequently reported (≥5%) AEs over time in study HS2AB3009 is presented in Table 27 below.

Table 27. Summary of Frequently Reported (≥5% Incidence in Any Treatment Group) Adverse Events in Source Partners Over Time (ITT Population)

	Month 0 to Month 4		End of Month 4 to Month 8[1]	
Adverse Event	**Placebo N=741 n**	**Valtrex N=743 n**	**Placebo N=634 n**	**Valtrex N=641 N**
Any Event	506 (68%)	540 (73%)	374 (59%)	374 (58%)
Event (n%)				
Headache NOS	164 (22%)	186 (25%)	88 (14%)	84 (13%)
Nasopharyngitis	79 (11%)	80 (11%)	60 (9%)	64 (10%)
URI* NOS	47 (6%)	47 (6%)	41 (6%)	32 (5%)
Diarrhea NOS	40 (5%)	51 (7%)	17 (3%)	19 (3%)
Nausea	44 (6%)	47 (6%)	10 (2%)	17 (3%)
Pharyngolaryngeal pain	43 (6%)	47 (6%)	24 (4%)	19 (3%)
Back pain	33 (4%)	42 (6%)	19 (3%)	25 (4%)

NOS = Not Otherwise Specified
URI = Upper Respiratory Tract Infection
[1] Source partners in study for ≥4 months

During the first 4 months of the study, 68% (506/741) of source partners in the placebo group and 73% (540/743) of source partners in the Valtrex group reported an AE. During the final 4 Months of the study, for source partners who were in the study for ≥4 months,

59% (374/634) in the placebo group and 58% (374/641) in the Valtrex group, reported an AE.

The incidence of AEs was similar between treatment groups, with headache, nasopharyngitis, and upper respiratory tract infection reported most commonly. There was no evidence of an increase in the overall incidence of AEs in the Valtrex group over time compared with the placebo group during the study. In fact, the incidence of AEs in both groups was lower in the last 4-month period of the study.

5.10. Additional safety data

Additional safety information on Valtrex obtained throughout the clinical development program is provided for reference in Appendices 5 through 8. Safety topics summarized within each Appendix are as follows:

Appendix 5	Safety and Efficacy of Valtrex as Suppressive Therapy for Recurrent Genital Herpes
Appendix 6	Acyclovir and Valacyclovir: Long Term Safety Experience
Appendix 7	Summary of Thrombotic Microangiopathies in Immunocompromised Patients treated with Valtrex
Appendix 8	Post-Marketing Experience: Spontaneous Reports of Serious Adverse Experiences and Death

6. OVERALL STUDY CONCLUSIONS

6.1. Efficacy Conclusions

Study HS2AB3009 utilized acquisition of symptomatic, laboratory confirmed genital HSV-2 infection in the susceptible partner as the primary endpoint, as prospectively recommended by FDA and agreed by GSK and investigators. The results of the study show a significantly lower frequency of symptomatic, laboratory confirmed genital HSV-2 infection in the Valtrex group (0.5%) compared with the placebo group (2.2%) (p = 0.011), representing a 75% reduction in the risk of transmission.

This positive effect of Valtrex on the primary endpoint is reinforced by results for multiple secondary endpoints in this study. Specifically:

- Time to clinical symptoms of genital herpes in the susceptible partner was significantly longer in the Valtrex group compared with the placebo group (HR = 0.25 [95% CI: 0.08, 0.75]; p=0.008).
- The proportion of couples with overall acquisition of genital HSV-2 infection (clinical plus asymptomatic acquisitions) was higher in the placebo group (3.6%) versus the Valtrex group (1.9%)(p = 0.054). Of note, the time to overall acquisition of HSV-2 was significantly shorter in the placebo group versus the Valtrex group (HR = 0.52 [95% CI: 0.27, 0.99]; p = 0.039).
- The proportion of couples with HSV-2 seroconversion in the susceptible partner was lower in the Valtrex group (1.6%) compared with the placebo group (3.2%)(p=0.060). Additionally, the time to HSV-2 seroconversion approached statistical significance in favor of Valtrex (HR = 0.53 [95% CI: 0.26, 1.07]; p=0.069).
- The viral shedding substudy showed a significant reduction in both asymptomatic and total HSV-2 shedding in the Valtrex group as compared with placebo, in terms of both the number of days on which virus was shed (p<0.001) and the quantity of virus shed (p=0.009).

Numerically, a lower frequency of HSV-2 transmission was observed with Valtrex, compared with placebo, for both male-to-female transmission and female-to-male transmission.

In addition to these effects related to HSV-2 transmission, Valtrex was significantly more effective than placebo in preventing clinical outbreaks of recurrent genital herpes as well as oral lesions:

- More placebo-treated source partners had genital HSV-2 recurrences than Valtrex-treated source partners (77% vs 39%). Time to first recurrence of genital HSV-2 in the source partner was significantly shorter in the placebo group compared with the Valtrex group (p<0.001).

- More placebo-treated source partners reported oral HSV outbreaks than Valtrex-treated source partners (17% vs 10%). Time to first oral HSV outbreak in the

source partner was significantly shorter in the placebo group compared with the Valtrex group ($p<0.001$).

The overall weight of evidence across the primary endpoint and this series of secondary endpoints consistently favors suppressive Valtrex therapy over placebo as providing significant clinical benefit, both in terms of the previously established efficacy in reducing the frequency of recurrent genital herpes episodes, as well as the effect on reducing transmission of genital herpes disease.

6.2. Safety Conclusions

The safety data collected during the double-blind phase of study HS2AB3009 are consistent with the well-characterized safety profile of Valtrex in immunocompetent adults. No new safety signals were identified.

- The nature and incidence of adverse events for source partners were similar between Valtrex and placebo groups, with headache, nasopharyngitis, and upper respiratory tract infection reported most commonly.

- Adverse events leading to treatment discontinuation occurred infrequently. Serious adverse events were reported infrequently and with similar frequencies in both treatment groups.

- No deaths were reported in the study.

In summary, Valtrex 500mg once daily was well tolerated in this study, consistent with the existing safety profile as reflected in the current product labeling.

7. DISCUSSION

In this discussion, we will briefly review the basis for Study HS2AB3009 and then summarize the major outcomes of the study, with particular attention to the concordance of evidence of efficacy across the primary endpoint and an array of secondary endpoints. We will then enumerate and comment on some potential medical/scientific questions about the study, in the interest of fostering the continuing dialogue with FDA and the Advisory Committee. Finally, we will review overall conclusions and discuss the implications of these data for patient management.

Basis for Study HS2AB3009

Currently, patients with genital herpes are advised by health care professionals, CDC guidelines, and service organizations (such as ASHA) to reduce the risk of HSV-2 transmission to a sexual partner by abstaining from sexual contact during periods with genital lesions or other symptoms of genital herpes, as well as using safer sex practices (including condoms), even during asymptomatic periods. This advice is based on evidence that individuals with genital herpes shed virus intermittently, even in the apparent absence of lesions [Wald 1995; Wald 1996; Koelle 2000], and that asymptomatic viral shedding is sufficient to transmit genital herpes to a sexual partner [Mertz 1985, Mertz 1992]. Condoms are incompletely effective in preventing transmission of genital herpes. A recent study identified a reduction in risk of genital herpes transmission associated with even intermittent condom use, although protection from acquisition was limited to susceptible women [Wald 2001]. However, it is clear from such studies that, despite counseling on the importance of safer sex, many couples in monogamous heterosexual relationships do not use condoms consistently [Wald 2001].

The objective of Study HS2AB3009 was to assess the effectiveness of suppressive Valtrex therapy (500mg once daily) compared with placebo, in addition to counseling on safer sex practices, to reduce the transmission rate of genital herpes in heterosexual, monogamous, HSV-2 discordant couples where the source partner was an appropriate candidate for suppressive therapy. All couples were counseled on safer sex practices at each monthly clinic visit, provided with standardized educational materials [Reitano 1997], and encouraged to practice safer sex, including using condoms during every sexual encounter with their partner.

Major Outcomes of Study HS2AB3009

A total of 1,498 source partners and their susceptible partners were randomized to the study over a 42 month enrollment period; 1484 took at least one dose of study drug and were included in the intent-to-treat analysis. The source partners were randomized to receive Valtrex 500mg once daily (n = 743) or placebo once daily (n = 741) in double-blind manner for 8 months. Demographics and baseline characteristics were similar across the two treatment groups. Consistent with expectation, the majority (67%) of source partners were female and they were equally balanced between treatment groups.

Analysis of the primary endpoint showed that the proportion of couples with clinical evidence of a first episode of genital HSV-2 infection in the susceptible partner was

reduced from 2.2% in the placebo group to 0.5% in the Valtrex group (p=0.011). Relative to placebo, the Valtrex group had a relative risk of 0.25 (95% CI: 0.08, 0.74), representing a reduction of 75% in the risk of transmission of symptomatic genital herpes. This magnitude of effect meets the prospective expectation set by prestudy discussions between GSK and FDA on the effect size that would constitute a meaningful clinical benefit and therefore strong evidence of efficacy. Furthermore, a Kaplan-Meier survival analysis of the time to primary endpoint, which confirmed the results of the primary endpoint proportions analysis, showed that couples appeared to be at continued risk of transmitting genital herpes over the 8 month double-blind phase and that couples in the Valtrex group continued to derive benefit from treatment throughout the eight-month duration of the study.

The viral shedding substudy provides additional, consistent evidence in strong support of the outcome of the main study, showing that Valtrex significantly reduces shedding of HSV-2. The mean asymptomatic and total shedding rates were significantly lower for the Valtrex group compared with placebo ($p < 0.001$). In addition, the proportion of subjects with at least one episode of HSV-2 shedding was significantly lower in the Valtrex group compared with placebo ($p = 0.002$). There were also reductions in the quantity of virus shed during Valtrex treatment: the overall log-transformed average number of HSV DNA copies per day and the log-transformed average number of HSV DNA copies per day on asymptomatic shedding days were also significantly lower in the Valtrex group compared with placebo ($p < 0.001$ and $p= 0.009$, respectively).

Data were collected on multiple secondary endpoints in study HS2AB3009. As shown in previous sections of this Briefing Document, there is strong evidence of concordance with the primary endpoint across this array of secondary endpoints. Specifically, the proportion of couples with overall acquisition of genital HSV-2 infection (including both symptomatic and asymptomatic acquisitions) was lower in the Valtrex group than placebo group ($p = 0.054$). Further, the time to overall acquisition was significantly longer in the Valtrex group compared with placebo ($p=0.039$), which reflects a 48% lower risk of acquiring HSV-2 infection in the Valtrex group compared with placebo at any time during the 8-month study period. Also, the proportion of couples with HSV-2 seroconversion in the susceptible partner was lower in the Valtrex group compared with the placebo group ($p = 0.060$). Additionally, the time to HSV-2 seroconversion was longer on Valtrex than placebo ($p = 0.069$).

Safety was assessed throughout the 8-month double-blind phase of this study, with continued assessment for patients who continued into the 12-month open-label extension. The safety profile of Valtrex in this study was similar to that of placebo, and similar to that reported previously with suppressive therapy in immunocompetent adults. The nature and incidence of adverse events were similar in the Valtrex and placebo groups, with headache, nasopharyngitis, and upper respiratory tract infection reported most commonly in both groups. Adverse events leading to treatment discontinuation and serious adverse events were reported infrequently in both treatment groups; no deaths were reported in the study. No cases of TTP/HUS were reported in the study, and laboratory data were similar across the treatment groups.

Potential Medical/Scientific Questions

GSK accepted a substantial medical/scientific challenge in endeavoring to collaborate with others to design, conduct, and report the results of this effort to demonstrate, for the first time, a beneficial effect of drug therapy for a source partner on sexual transmission of a viral infection to their susceptible partner. Now that the study has been completed and analyzed, we recognize a number of the potential medical/scientific questions about the study. In the section below, we have enumerated and commented on these topics in the interest of fostering the continuing dialogue with FDA and the Advisory Committee.

Single, Controlled, Clinical Trial

FDA, the Advisory Committee, and sponsors are well aware of FDA's informative guidance document on clinical evidence of effectiveness, including guidance on situations in which evidence from a single adequate and well-controlled trial can comprise substantial evidence of effectiveness (Food and Drug Administration. *Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.* May 1998). GSK believes that study HS2AB3009 meets the standards described in the guidance document for the following reasons:

- Study HS2AB3009 was a large, multicenter trial in which no single center provided an unusually large proportion of patients and in which the primary endpoints were distributed across multiple centers in the US, Canada, and Australia.

- Study HS2AB3009 is clinically persuasive and statistically significant (with a 75% reduction in the relative risk of transmission as measured by the primary endpoint), in the context of a prospectively discussed expectation that an approximately 70-80% reduction in relative risk would comprise a meaningful result for this study.

- Study HS2AB3009 yielded consistent evidence of superior efficacy of Valtrex over placebo across multiple endpoints. Specifically, the primary endpoint and majority of secondary analyses were statistically significant or approached statistical significance in favor of Valtrex, providing consistent evidence of a superior treatment effect of Valtrex over placebo.

- The viral shedding substudy conducted as part of Study HS2AB3009 showed significant reduction in shedding (number of days with shedding and number of HSV DNA copies) in the Valtrex treatment group compared with placebo. These data confirm prior study results demonstrating reduction of shedding frequency by Valtrex. As viral shedding from the skin is an important reservoir for HSV-2 transmission, this substudy provides further strong supporting evidence of the efficacy of Valtrex.

- The evidence of a beneficial effect of Valtrex on HSV-2 transmission in study HS2AB3009 is supported by other, independent evidence from adequate and well-controlled trials of the efficacy of Valtrex for suppression of recurrent episodes of genital herpes. Importantly, the additional evidence from those trials

includes a demonstration of the efficacy of suppressive therapy over a 12 month double-blind period using the same dosage regimen (500mg once daily) in the same patient population (i.e., immunocompetent adults with a history of ≤ 9 episodes of genital herpes per year) as the Valtrex-treated source partners in study HS2AB3009.

Asymptomatic Acquisition of HSV-2

In study HS2AB3009, the only inconsistent finding among secondary endpoints was the observation that the frequency of asymptomatic HSV-2 seroconversion was not significantly different in the Valtrex (1.3%) and placebo groups (1.5%). In addition, the times to asymptomatic seroconversion in the Valtrex and placebo groups were not significantly different. It should be noted that this population comprises a subset of the overall acquisition population and that this analysis was provided in the interest of completeness. The issue of acquisition of symptomatic disease versus asymptomatic infection has been discussed within the context of prophylactic vaccine development, where it has been theorized that immunization may protect against clinical disease, but that serum antibodies may not afford protection from initial mucosal infection by HSV-2 and subsequent latency [Stanberry 2000]. Although it has been theorized that Valtrex treatment may reduce, quantitatively, the level of virus below that able to establish a symptomatic infection, in fact, the relationship between the amount of viral inoculum and the host immune response in establishing clinical disease has not been defined. Obviously, both virus and host factors are important determinants of whether infection with HSV-2 is ultimately manifested clinically, and there is more to learn to fully understand this observation. Nonetheless, it is noteworthy that time to overall acquisition was significantly longer in the Valtrex group compared to placebo (p=0.039).

Discontinuation of Patients

The importance of collecting complete data in clinical trials, and minimizing patient discontinuations and missing data, is well recognized. These concerns were prospectively recognized by GSK and investigators for study HS2AB3009, in part due to the number and frequency of clinic visits in this study, as well as the extent of intimate, personal information being collected from couples in this study. GSK was prospectively concerned that the intrusiveness of the study would comprise a barrier to subjects' participation, and efforts were made during recruitment to enroll couples who understood the demands of the study and were committed to durable participation.

Overall, in study HS2AB3009, the patient discontinuation rate was 22%. However, it is reassuring to note that the pattern of dropouts was similar between the Valtrex and placebo groups (21% and 22%, respectively) and that some data were available from 96% of the subjects in the ITT population during the course of the study. The similar dropout pattern supports the assumption that discontinuation occurred independent of treatment and the balance between treatments is consistent with maintenance of the blind throughout the study. Also, for your information, it is noteworthy that the recent large vaccine studies of ambulatory patients or couples with genital herpes were conducted with approximately 20% of subjects discontinuing in vaccine and placebo groups in each of these studies, as summarized in Table 28.

Table 28. Rate of Discontinuation from Randomized, Double-Blind, Placebo-Controlled Vaccine Studies

Study	Discontinuation Rate	
	Placebo	Vaccine
Two 18 month studies of the Chiron vaccine [Corey 1999a]	261 / 1195 (21.8%)	286 / 1198 (23.9%)
19 month Study 1 of GSK vaccine [Stanberry 2002]	69 / 422 (16.4%)	81 / 425 (19.1%)
19 month Study 2 of GSK vaccine [Stanberry 2002]	189 / 944 (20.0%)	188 / 923 (20.3%)

In situations like this where the discontinuation rate is relatively high, time-to-event analysis is a useful approach since it explicitly allows for differential length of follow-up of subjects. Importantly, this analysis leads to virtually identical results to the primary analysis of proportions, providing reassurance that discontinuations did not undermine the validity of the study.

The impact of missing data on efficacy was also carefully evaluated. Sensitivity analyses were performed to explore the robustness of the efficacy outcomes in the face of various ways of handling missing data. Of these analyses, the most intuitively appealing is the sensitivity analysis where missing endpoints in both treatment groups are imputed at the overall placebo rate. The result of this sensitivity analysis is consistent with the primary analysis of the study and provides further support for superiority of Valtrex over placebo.

Termination of the Study

Study HS2AB3009 (as amended) was designed to run until 28 primary endpoints were accrued. Assuming 3% and 0.75% frequencies of transmission of HSV-2 in the placebo and Valtrex groups, respectively, the enrollment objective of the study was a total of 1,500 couples. In May 2001, a decision was made to stop recruitment into the study when 1500 couples had been enrolled. The study was then terminated in July 2001 after that goal was achieved (a total of 1498 couples were enrolled). The study was completed in March 2002 after the last patient's final visit. At the time of termination, the study had accrued an estimated 23 endpoints (based on ongoing informal review by the EPC). Sufficient patients were ongoing to support a projection that the study would attain 28 primary endpoints. However, following completion of patients and review of all referred cases by the Endpoint Committee, 20 primary endpoints were the result.

At the outset, it is noteworthy that expansion of this study beyond 1,500 couples in order to accrue additional endpoints would have been highly impractical. The study required an extended period of time (3.5 years) to accrue 1,498 couples, placing a strain on study sites and personnel. In addition, in 2001, GSK regularly received feedback from investigators that identification of new couples for enrollment was becoming increasingly difficult.

We recognize that the study did not accrue the prespecified number of primary endpoints. Nonetheless, the 20 primary endpoints and their marked split between the placebo group (16 primary endpoints) and Valtrex group (4 primary endpoints) do merit interpretation

of this study. In view of the substantial challenge of conducting this unique study, we should learn as much as possible from it.

Extrapolation to Other Populations

Study HS2AB3009 was designed for conduct in monogamous, heterosexual couples because this setting is one where GSK and investigator/consultants believed an adequate and well-controlled clinical trial could most likely be conducted. This study population is free of the potential confounding effect of transmission of HSV-2 from a non-study source partner to a non-monogamous susceptible partner. Couples in this study were expected to have a relatively high commitment to complying with study procedures.

GSK fully recognizes that the efficacy of Valtrex for reducing transmission of genital herpes has not been established in individuals with multiple partners, non-heterosexual couples, and couples not counseled to use safer sex practices, and we have proposed draft labeling that explicitly states this limitation.

Frequency of Endpoints and Number Needed to Treat

The rate of HSV-2 transmission observed in the control arm in this study was relatively low compared to the limited published reports, with acquisition of genital herpes disease noted in 2.2% of susceptible subjects in the placebo group over the 8 month study period (previously published studies have reported annual transmission rates of approximately 3-10%, depending on the population studied, the criteria used to define transmission, and the study duration). There are several likely reasons for the relatively low frequency of endpoints observed in Study HS2AB3009:

- Monogamous heterosexual partners may represent a lower risk population for transmission compared with the general population.

- Couples in the study were provided with extensive counseling regarding safer sex practices.

- The protocol allowed source partners who had a recurrent episode of genital herpes to receive open-label Valtrex treatment (500mg twice daily for 5 days), potentially reducing the number of transmissions that might have occurred during symptomatic periods.

- Susceptible partners were primarily male.

This latter point is particularly relevant in view of the historically greater susceptibility of females to HSV-2 acquisition. This observation was borne out in this study, in which (despite enrollment of approximately twice as many male susceptible partners as females), more female than male susceptible partners acquired genital HSV-2, either clinically or asymptomatically.

A consequence of the relatively low frequency of HSV-2 transmission in this study is that a drug-related reduction in the frequency results in a relatively large "number needed to treat" (NNT). Based on the primary endpoint in study HS2AB3009, approximately 62

subjects would need to take suppressive Valtrex therapy over an 8 month period to prevent one case of genital herpes transmission. Assuming that the transmission rate in both treatment groups remains constant over time, this would represent an annualized NNT of 41. However, other factors must be considered to understand the context for this NNT. First, treated source partners are receiving Valtrex for suppression of genital herpes and thereby directly benefit from a clinically and statistically significant reduction in the frequency of recurrent episodes of genital herpes. For the source partner, a reduction in the risk of transmission is therefore an *additional* benefit, beyond the benefit of a reduced frequency of recurrent episodes. Second, the study population in HS2AB3009 was at relatively low risk for transmission of genital herpes. The study recruited more male susceptible partners than female, while transmission rates were clearly higher to female susceptible partners. Also, a monogamous heterosexual population may be at lower risk of transmission than non-monogamous, non-heterosexual populations. If the same relative risk reduction with Valtrex is applied to the general population, where the transmission rates are likely to be higher, then a smaller NNT value would be obtained.

Gender of Source Partner

Study HS2AB3009 was not designed or powered to assess, independently, the effects of Valtrex versus placebo on (1) transmission from male source partner to female susceptible partner and (2) transmission from female source partner to male susceptible partner. Nonetheless, the effects of Valtrex versus placebo were examined, by gender of the source partner, in secondary analyses. Valtrex was associated with a numerically lower frequency of transmission of HSV-2 than placebo, regardless of gender of the source partner. With respect to transmission from a male source partner to a female susceptible partner, primary endpoints of HSV-2 transmission occurred for 0.8% and 4.1% of individuals in the Valtrex and placebo groups, respectively. With respect to transmission from a female source partner to a male susceptible partner, primary endpoints of HSV-2 transmission occurred for 0.4% and 1.2% of individuals in the Valtrex and placebo groups, respectively. GSK recognizes that the numbers of cases are small in some cells of this assessment.

Inconsistent Use of Condoms

Study HS2AB3009 included counseling of all couples on safer sex practices, including encouragement to use condoms, even during asymptomatic times. As in other studies reported in the literature, the extent of use of condoms was variable during this study. Approximately half of the susceptible partners in both the placebo and Valtrex groups (49% and 51%, respectively) reported "never" using condoms during sexual relations during the month prior to enrolling in the study. During the study, all couples were encouraged to use condoms during all sexual contacts, and were offered condoms at each monthly clinic visit. Patient diary records showed that 55-57% of couples reported "never" using condoms during the study. Approximately 30% of susceptible partners in both treatment groups reported that condoms were "nearly always" used (i.e., > 90% of the time) during vaginal sexual contacts. Approximately 20-25% of susceptible partners in each treatment group reported condom use "nearly always" during anal sexual contacts during the study.

Recognizing the variable use of condoms during the study, a secondary analysis was conducted where the primary endpoint was assessed within each of the three strata of condom use ('never', 'sometimes', or 'nearly always'). It is noteworthy that Valtrex showed superior efficacy to placebo in reducing HSV-2 disease transmission across all three strata of condom use. Specifically, for the stratum for condom use 'nearly always,' primary endpoints of HSV-2 transmission occurred for 0% and 1.4% of individuals in the Valtrex and placebo groups, respectively. For the stratum for condom use 'sometimes,' primary endpoints of HSV-2 transmission occurred for 0% and 2.0% of individuals in the Valtrex and placebo groups, respectively. For the stratum for condom use 'never,' primary endpoints of HSV-2 transmission occurred for 1.0% and 2.8% of individuals in the Valtrex and placebo groups, respectively.

It is notable that even among susceptible partners who reported that condoms were 'nearly always' used, 3 of 212 individuals (1.4%) in the placebo group nonetheless acquired symptomatic genital herpes. These documented cases of HSV-2 transmission, despite use of condoms, are consistent with other reports in the literature that suggest that condoms are incompletely effective. Some authors have addressed the concerns that have arisen over relying on barrier methods alone to prevent transmission [Adam 2001], especially in heterosexual monogamous couples in long-term relationships who are often reluctant to use condoms. This observation reinforces the importance of emphasizing concurrent use of counseling, safer sex practices, and suppressive therapy with Valtrex.

Overall Conclusions and Implications for Patient Management

This study establishes that Valtrex, in combination with safer sex counseling, reduces the risk of heterosexual transmission of genital herpes disease in immunocompetent adults, compared with safer sex counseling alone. Thus, patients receiving suppressive therapy with Valtrex, when combined with counseling on safer sex practices, benefit from both a reduced rate of HSV recurrences and a reduced risk of transmission of genital herpes to their susceptible partner. Suppressive therapy with Valtrex offers an important additional means of reducing the risk of transmission of genital herpes. Valtrex Caplets can be a valuable treatment option for reducing transmission of genital herpes, particularly during the period of years when no prophylactic vaccine with proven efficacy against herpes viruses is available. In order to use this strategy effectively, it should be part of a comprehensive healthcare program that involves identifying and counseling HSV-2 discordant couples on the risk of transmission and the importance of safer sex practices.

The decision to initiate suppressive Valtrex treatment in a given individual (to provide the dual benefit of reduced genital herpes recurrences and reduced risk of transmission in the context of safer sex counseling) is one that must be made on a case-by-case basis following discussion between the patient and his/her healthcare professional. To support the identification of appropriate candidates for suppressive therapy, Section 8 of this document further discusses the benefit/risk equation of suppressive Valtrex therapy, while Section 9 describes approaches recommended by GSK for communicating to patients and healthcare professionals who are receiving/prescribing suppressive therapy, or who are considering doing so.

8. BENEFIT/RISK RELATIONSHIP

8.1. Patient concerns

Some clinicians have historically considered genital herpes to be of relatively minor clinical importance. However, this attitude seems increasingly uninformed when the physical morbidity, psychosocial impact, and potentially serious consequences of the disease are considered. On an individual basis, episodes of genital herpes can cause substantial pain and discomfort. In addition, the disease may have a profound psychological and social impact on an individual and is often associated with feelings of anxiety, shame, depression, isolation, frustration about interference with sexual activity, aggravation concerning the recurrence of symptoms, fear of rejection by a partner and fear of transmission to a partner [Mindel 1993; Mindel 1996; Carney 1993]. Studies indicate that these concerns do not dissipate substantially over time [Carney 1993; Carney 1994] and that, although suppressive therapy can provide some relief from anxiety, genital herpes sufferers continue to experience considerable psychological morbidity [Carney 1994].

On a broader scale, the potentially serious complications of HSV-2 infection can have significant public health impact, primarily in terms of the rare but potentially devastating effects of neonatal herpes as well as the increasingly recognized facilitative effect afforded by HSV-2 infection with regard to increased risk of transmitting and acquiring HIV. Collectively, these factors position genital herpes second only to HIV as the STD of greatest concern to sexually active individuals [Catotti 1993; Corey 1999b; Handsfield 2001]. The National STD Hotline, funded by the CDC, provides a quantitative measure of this concern: the Hotline receives about 60,000 herpes-related calls annually, more than for any other single STD and almost as many as for all other STDs combined [Corey 2000].

8.2. Additional benefit of suppressive therapy

The scenario in which a HSV-2 seronegative susceptible partner may derive benefit from a therapy taken by his/her HSV-2 seropositive partner is somewhat unique. Under most circumstances, the balance of benefit versus risk for a given drug is weighed within a single individual who is receiving that drug. However, in the case of suppressive Valtrex therapy taken by a source partner who is in a monogamous, heterosexual HSV-2 discordant relationship, the benefit to the susceptible partner in terms of reduced risk of HSV-2 acquisition is in addition to the benefit demonstrated for the source parter, i.e., reduction in frequency of genital herpes recurrences. Importantly, this additional benefit in the susceptible partner is gained with no increase in drug-related risks to the source partner.

This Supplemental NDA requests that the labeling for Valtrex Caplets be revised to state that suppression of recurrent episodes of genital herpes (in the context of safer sexual counseling) in the source partner of a monogamous, heterosexual, immunocompetent couple are associated with a reduction in the risk of transmission of HSV-2 to the susceptible partner. Quantitatively, with respect to the prospectively defined primary

endpoint (i.e., acquisition of clinical signs and symptoms of genital herpes) in study HS2AB3009, transmission of HSV-2 was reduced from 2.2% of individuals in the placebo group (n=741) to 0.5% of individuals in the Valtrex group (n=743) during 8 months of suppressive therapy (p=0.011); this reduction represents a 75% decrease in the relative risk of HSV-2 transmission. Quantitative application of these results to the study population shows that symptomatic acquisition of HSV-2 could be reduced from 22 cases to 5 cases per 1,000 susceptible partners per 8 months of suppressive therapy with Valtrex in concert with safer sex counseling. The proportion of susceptible partners who acquired HSV-2 infection (symptomatic and asymptomatic) was reduced by 48% in the Valtrex group (p=0.054).

An alternative method of analysis is by 'time to event', which explicitly allows for differential length of follow-up. The time to clinical acquisition and time to overall acquisition of HSV-2 in the susceptible partner were significantly reduced in the Valtrex group during 8 months of suppressive therapy in concert with safer sex counseling (p=0.008 and p=0.039, respectively). For time to clinical acquisition, the difference in estimated proportions between the Valtrex and the placebo groups at 8 months was 1.8%. These results show that at any time during the 8-month study period, subjects in the Valtrex group had a 75% lower risk of acquiring symptomatic genital herpes compared with placebo. Similarly, for time to overall acquisition, the difference in estimated proportions between the Valtrex and the placebo groups at 8 months is 2.2%, which reflects a 48% lower risk of acquiring HSV-2 infection compared with placebo at any time during the 8-month study period. The reductions in time to clinical and overall HSV-2 acquisitions were statistically significant and, from our perspective, are also clinically meaningful.

Importantly, and consistent with previous studies, Valtrex also provided benefit to the source partner by significantly prolonging the time to recurrence of genital herpes compared with placebo. This suppressive benefit of Valtrex has been demonstrated in a previous, large, randomized, double-blind, placebo-controlled study, as summarized in the current FDA-approved labeling (see Appendix 9) and as described in Appendix 5 of this document. Few patients (7%) receiving placebo for 6 months remained recurrence-free, while 55% of patients on a suppressive regimen of Valtrex (1000 mg once daily) remained recurrence-free through 6 months. Of particular relevance in view of the 500 mg once daily suppressive Valtrex regimen used in the HS2AB3009 study population, the previous trial also demonstrated significant benefit over placebo of the 500 mg once daily dose in patients with ≤9 recurrences per year (52% recurrence-free after 6 months of Valtrex treatment vs 7% in the placebo group [GSK Document BQRT/96/0001], and 31% recurrence-free after 12 months of Valtrex vs 2.9% in the placebo group) [GSK correspondence to FDA, 24 February 1997]. These data provide confirmatory evidence of the appropriateness of this dose as suppressive therapy in patients with 9 or fewer recurrences each year.

This benefit and the clear quantitative difference from placebo comprises substantial evidence of the benefit of suppressive therapy in markedly increasing the proportion of patients who remain free of recurrent episodes of genital herpes for a given time. The observations in study HS2AB3009 are fully consistent with these benefits of suppressive therapy with Valtrex. Over the 8 month treatment period, Valtrex significantly prolonged

the time to first recurrence of genital herpes compared with placebo. Further, for the 8 month period, a much larger proportion of patients in the Valtrex group (47%) than placebo group (13%) were recurrence free. This suppressive benefit of Valtrex is statistically significant and clinically meaningful. Further, the currently approved status of suppressive therapy with Valtrex shows that the benefit/risk calculus for suppressive use of Valtrex is favorable in immunocompetent patients.

Now, with this Supplemental NDA, GSK is describing an additional benefit of suppressive therapy with Valtrex, with no change to drug-associated risks. In our view, the reduction in transmission shown in study HS2AB3009 comprises substantial evidence of an additional benefit of suppressive therapy with Valtrex. The safety data collected in HS2AB3009 are similar for Valtrex and placebo, consistent with the same, well-characterized safety profile of Valtrex in immunocompetent adults. No new safety signal was identified in this study or in a review of postmarketing surveillance reports. Therefore, GSK is submitting this Supplemental NDA to request the addition of information on this new, incremental benefit of suppressive therapy to labeling. In GSK's view, the new information strengthens the benefit/risk profile of suppressive therapy with Valtrex Caplets even more in favor of benefit.

9. PLANS FOR COMMUNICATION WITH HEALTH CARE PROFESSIONALS AND PATIENTS

9.1. Experience with safer sex counseling

As previously discussed, NHANES III survey data demonstrated that HSV-2 seroprevalence in the US in persons over the age of 12 years increased from approximately 16% to 22.0% between 1978 and 1991, a rise of over 30% during a decade of concerted safer sex promotion efforts [Fleming 1997]. In 1998, following the publication of these data, the US CDC convened a special consultants' meeting to consider how the public health sector should respond to the challenge of this viral STD [Handsfield 1999]. Among the panel's recommendations was a more aggressive effort to educate both the general public and healthcare providers about genital herpes and safer sex practices to prevent transmission [Handsfield 1999]. The panel recognized the challenges of such a program for the patient and the medical professional providing the counseling. Unfortunately, no national program resulted from the meeting, nor has there been any standardized, national program instituted in recent history for prevention of genital herpes. Furthermore, the results of local counseling and educational programs for genital herpes as part of a disease management program have also not been reported in the literature. Thus, the sexual practices of patients with genital herpes and the effect of a disease management program emphasizing safer sex practices are largely unknown.

However, local counseling does appear to be occurring. Recently, ASHA conducted a survey of 394 newly diagnosed genital herpes patients to gather information regarding patient counseling [Gilbert 2002]; these data, albeit limited, provide a credible profile of current education and counseling practices. Generally, more than 75% of patients received some education/counseling from their healthcare providers, a proportion similar to those receiving prescriptions for antiviral medication. The amount of time dedicated to this function varied considerably, however, with the vast majority of patients reporting that education/counseling occupied less than 11 minutes of clinic time. The survey indicated that only 45% of patients reported any follow-up visit.

The majority of patients (range, 89.0–100%) thought that education and counseling were somewhat or very important to cover in the first 6 months of diagnosis. Table 29 summarizes the percent of patients receiving various educational resources on genital herpes from their provider.

Table 29. Percent of Genital Herpes Patients Receiving Educational Resources from Provider [1]

Educational Resource/Referral	Percentage of Patients Receiving Information
Brochures/newletters	51.1%
Telephone hotlines	17.0%
Internet websites	11.4%
Books	7.9%
Support groups	6.8%
Referrals to other providers	5.6%
Videos	3.6%
CD-ROMs	1.8%

1. Gilbert 2002

In addition to the resources provided by providers, over 90% of patients reported seeking out additional information on their own. Table 30 summarizes the media or information sources used for patients' search activities.

Table 30. Resources Used by Patients for Gathering Information About Genital Herpes [1]

Resource/Activity	Percentage of Patients Reporting Use
Exploring Internet/websites	53.0%
Calling toll-free number seen on TV ad	49.5%
Reading magazine or book	47.0%
Conducting library search	30.7%
Talking with friend or family member	22.8%
Calling a hotline	19.5%

1. Gilbert 2002

Despite the availability of these resources, however, nearly all (95.0%) thought that they would contact a trained health educator with genital herpes expertise in person, by phone, or both, if access were offered.

Of those who reported receiving education and counseling following a genital herpes diagnosis (approximately 75% of patients in the survey), the majority reported that this education and counseling was provided by physicians (45%), followed by physician's assistants/nurse practitioners (21%) and nurses (14%), respectively. Topics clustered around two subjects: clinical/epidemiological factors and psychosocial/behavioral factors. Patients reported that healthcare providers were more likely to discuss factual (clinical) topics rather than emotional (psychosocial) topics. When asked for suggestions for improving genital herpes education and counseling from healthcare providers, respondants indicated that they wanted more information, more resources and greater emotional support from their provider(s). Patients also wanted their providers to address feelings, such as embarrassment and isolation, to discuss prevention of HSV-2 transmission to a partner, and to engage in non-judgmental communications.

9.2. Experience with safer sex practices

As mentioned previously, the primary methods for safer sex practices are education about the disease and transmission, condom use and abstinence. Recommendations for consistent condom use have been made, yet condoms are used in a minority of the general population [Catania 1992, Catania 1995, Anderson 1999, CDC Guidelines 2002]. Only recently has it been demonstrated that condoms can markedly reduce the risk of acquisition of HSV-2 [Wald 2001]; however, in this study protection from HSV-2 acquisition was limited to women. The efficacy of condom use in preventing HSV-2 transmission in men requires further study.

There are sparse data about safer sex practices in people with genital herpes, where the risk of a susceptible partner acquiring genital herpes in a monogamous relationship ranges up to 10% per year a couple is together [Mertz 1992; Bryson 1993]. Data from Study HS2AB3009 showed that, despite counseling on safer sex practices and use of condoms, 55-57% of couples reported 'never' using condoms while on study. Behavioral data on condom use has also been gathered in an analysis of a large, randomized, controlled clinical trial of an HSV-2 vaccine in HSV-2 discordant monogamous couples [Wald 2001]. During this trial, condom use was low, as only 61% of couples reported ever using condoms during follow-up, despite counseling at each clinic visit. In couples who did report condom use, only 13% used condoms for each sexual act, while 49% used condoms during less than 25% of sexual acts. Despite repeated counseling, the use of condoms declined from 27% to 21% of sexual acts over the course of the study. Women at risk for HSV-2 acquisition were more likely to report condom use by their partners than were men at risk, with mean condom use during follow-up reported for 30% of sexual acts for women vs 20% for men. On a positive note, the proportion of participants engaging in sexual activity when the source partner had recognized genital lesions declined from 20% to 13% over the study period. However, on balance these data point to the need for continuing educational initiatives to emphasize the importance of safer sexual practices.

9.3. Plans for communicating with healthcare professionals and patients

GlaxoSmithKline recognizes that this Supplemental Application has implications for communication with health care professionals and patients. If the results of Study HS2AB3009 are incorporated into labeling as proposed, they merit appropriate consideration by health care professionals for use in patient counseling. GlaxoSmithKline recognizes the importance of participating (along with health care professionals, governmental agencies, and public service organizations) in efforts to provide educational information on genital herpes. In alignment with recent CDC Guidelines [CDC Guidelines 2002], this information should include content on the herpes virus, signs and symptoms of genital herpes, mode of acquisition of genital herpes, episodic and suppressive therapy, and prevention of sexual and perinatal transmission. The CDC Guidelines on sexually transmitted diseases are clear in this regard:

> "Counseling of infected persons and their sex partners is critical to management of genital herpes. Counseling has two main goals: to help

> patients cope with the infection and to prevent sexual and perinatal transmission. . . . Numerous resources, including the CDC National STD/HIV Hotline (tel: 800-227-8922), web sites (http://www.ashastd.org), and printed materials are available to assist patients and clinicians in counseling."

The importance of counseling is not diminished by the results of Study HS2AB3009. In fact, GlaxoSmithKline believes that the importance of counseling is increased by these results for the following reasons:

- This study shows a treatment effect of Valtrex in the setting of safer sex counseling (including use of condoms). Importantly, counseling emphasized that suppressive therapy with Valtrex is not a cure for genital herpes, nor is it an alternative to safer sexual practices and use of condoms. Moreover, subjects were advised that latex condoms, when used consistently and correctly, can reduce the risk of transmission of genital herpes when the infected areas are covered or protected by the condom.

- This study shows a treatment effect in a specific study population (monogamous, heterosexual, immunocompetent couples). The efficacy of Valtrex in other populations has not yet been demonstrated. Indeed, safer sex practices include limiting the number of different sexual partners.

- This study does not diminish the importance of advising patients to abstain from sexual activity with an uninfected partner when lesions or prodromal symptoms are present.

- This study does not diminish the importance of informing patients that sexual transmission of HSV can occur during asymptomatic periods.

Indeed, the public health content of these points is entirely consistent with the content of the CDC Guidelines on counseling patients with genital herpes. Further, information on Valtrex Caplets can be prepared and provided to health care professionals and, as appropriate, patients. In order to discern what information is appropriate, we must first consider contemporary use of antiviral drugs for the treatment of genital herpes and the specific health care professionals who care for these patients.

9.3.1. Current genital herpes treatment practices

Currently, in the United States, three prescription drug products are approved for episodic or suppressive therapy of genital herpes. These products are listed in Table 31 below:

Table 31. Antiviral Prescription Drugs Approved for Treatment of Genital Herpes

Product	Manufacturer	Date of First Approval in the US
Zovirax (acyclovir) products	GlaxoSmithKline	Ointment: March 29, 1982 Sterile Powder for Injection: October 22, 1982 Capsules: January 25, 1985 Suspension: December 22, 1989 Tablets: April 30, 1991
Acyclovir products	Several suppliers	April 22, 1997
Famvir (famciclovir) Tablets	Novartis	June 29, 1994
Valtrex (valacyclovir) Caplets	GlaxoSmithKline	December 15, 1995

These products are indicated for treatment of recurrent episodes or suppressive therapy. In terms of suppressive therapy specifically, CDC Guidelines provide the following direction:

> "Suppressive therapy reduces the frequency of genital herpes recurrences by 70%–80% among patients who have frequent recurrences (i.e., >6 recurrences per year), and many patients report no symptomatic outbreaks. Treatment probably is also effective in patients with less frequent recurrences, although definitive data are lacking. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years, and with valacyclovir or famciclovir for 1 year. Quality of life often is improved in patients with frequent recurrences who receive suppressive compared with episodic treatment."

Ongoing treatment occurs in only about half of the patients diagnosed with genital herpes. Among those treating, suppressive therapy is used infrequently when compared to episodic therapy. Table 32 summarizes the current profile of antiviral therapy for genital herpes in the US:

Table 32. Profile of antiviral therapy for genital herpes in the US (estimated data for CY2002)

Population	Number of Patients*
Patients diagnosed with genital herpes	9.6 million
Patients receiving any antiviral therapy (episodic or suppressive) for genital herpes	4.6 million
Patients receiving episodic therapy for genital herpes (with any antiviral drug)	3.4 million
Patients receiving suppressive therapy (with any antiviral drug)	1.2 million
Patients receiving suppressive therapy (with Valtrex)	0.54 million

* GSK estimates derived from NHANES III data and Scott Levin Source Data, 2002; calculations are based on an estimated 63 million patients with genital herpes in the US.

As shown in the table above, in 2002, approximately 540,000 patients received suppressive therapy with Valtrex. This figure comprises approximately 12% of the total

patients receiving any prescription drug therapy for genital herpes, and only 6% of all diagnosed genital herpes patients.

It is instructive to also examine the health care professionals who care for and prescribe medicine (Valtrex) for these patients. Table 33 summarizes the data.

Table 33. Profile of Prescribers/Health Care Providers for Patients with Genital Herpes in the US (December 2001 – November 2002) [1]

Health Care Professional	Number (%) Who Prescribed Valtrex in Last 12 Months
Primary care physicians (Internal Medicine, Family Practitioners)	120,082 (39% of total PCPs)
Obstetrics/Gynecology physicians	29,412 (51% of Ob/Gyns)
Dermatology physicians	8,173 (64% of Derms)
Infectious disease physicians	2,324 (37% of IDs)
Other physicians [2]	105,196
TOTAL PHYSICIANS	**265,187 (20% of all physicians)**
Physician Assistants	Less than 1% of total prescriptions captured
Nurse Practitioners	Less than 1% of total prescriptions captured

1 Scott Levin Data, 2002.
2 "Other physicians" consists of physicians from diverse medical specialities; no single speciality prescribes >1% of the total prescriptions captured.

Valtrex Caplets are most often obtained by prescription in a community-based pharmacy. There are over 55,500 retail pharmacies in communities throughout the United States with approximately 112,000 pharmacists practicing in these pharmacies.

9.3.2. Healthcare professional communication

For patients who are candidates for suppressive therapy, Study HS2AB3009 shows an additional benefit, i.e., reduction in the risk of transmission of genital herpes. Therefore, in considering potential audiences for communication, the most important audiences are health care professionals currently prescribing suppressive therapy or who are considering offering suppressive therapy as an option to their patients. In addition, because patients may direct their questions to pharmacists when their medication is dispensed, it will be important to include them as an audience in this communication plan. Paramount to any discussion on the reduction of transmission with Valtrex suppressive therapy is the fact that daily suppressive therapy must occur in conjunction with safer sex counseling, including discussions around abstaining from sex when a lesion is present and using condoms during sexual acts between outbreaks. To this end, GlaxoSmithKline intends to communicate such counseling recommendations to health care professionals as part of its launch activities, pending a favorable review of the supplemental NDA.

Some genital herpes patients seek treatment at STD clinics. In addition to reaching the prescribers working in these clinics via communication directly targeting health care professionals, we will also attempt to reach the STD clinics by including the National Coalition of State STD Directors in our communication plan.

9.3.3. Patient communication

For a number of years GlaxoSmithKline has been a strong supporter of genital herpes disease education materials for patients. This information has been provided in a variety of formats, including patient brochures and patient-based websites. In addition, GlaxoSmithKline provides independent grants to various third parties, including ASHA and WebMD, to support patient disease state information on genital herpes. Current disease state information included in materials distributed by GlaxoSmithKline advises patients on how the virus is transmitted, as well as on safer sex practices including abstinence from sex during an outbreak and use of a condom between outbreaks.

Pending a favorable review of the Supplemental NDA, GlaxoSmithKline intends to build upon the disease state information already provided to patients. Specifically, GlaxoSmithKline plans to develop and provide access to patient information that communicates the need to continue to employ safer sex practices when using Valtrex suppressively for the benefit of transmission reduction. GlaxoSmithKline plans to test these specific message points with patients to ensure they comprehend the information as presented.

Having considered the nature of the healthcare professionals and patients, as well as settings where patients will receive care and pharmacies where the product will be dispensed, we have enumerated a set of communications that are intended to address the various audiences, using print and internet as media, in a timely manner. These communications are also intended to be complementary to parallel efforts by governmental agencies (e.g., FDA, CDC) and public service associations (ASHA). The specific items are summarized in Table 34 on the following page. Taken together, we believe that they comprise a reasonable, appropriate, and responsible plan for providing information secondary to a favorable regulatory action on this application.

Table 34. Communication Plan Pending a Favorable Review of the Supplemental NDA for Valtrex Caplets

Item	Target Audience	Description	Method of Distribution
Health Care Professional Announcement	• All known prescribers of antiviral drugs for genital herpes • All community pharmacists • National Coalition of State STD Directors	• Letter to directly inform prescribers of results of Study HS2AB3009 and change in labeling for Valtrex in envelopes marked IMPORTANT PRESCRIBING INFORMATION. • Provide copy of FDA-approved labeling for Valtrex. • Reinforce the importance of counseling patients on safer sex practices (including use of condoms)	• Direct mail • Posting letter on FDA MedWatch internet site • Provide letter to ASHA and CDC for use at their discretion
Internet posting	• Health care professionals	• Published results of HS2AB3009 • Full Prescribing Information for Valtrex • Commentary to reinforce the importance of counseling patients on safer sex practices (including use of condoms) • Link to www.ashastd.org for counseling information	• Post on GSK valtrex.com health care professional website • Provide to independent health care websites for health care professionals to post at their discretion
Internet posting	• Patients	• Specific commentary, in lay terms, on how genital herpes is transmitted and the need to continue to employ safe sex practices when using Valtrex suppressively for the benefit of reducing transmission. • Includes Patient Friendly PI. • Link to www.ashastd.org for counseling information	• Post on GSK valtrex.com patient website • Provide to independent health care websites for consumers to post at their discretion
Information for Patients (i.e., patient-friendly package insert)	• Patients	• Patient friendly patient information will be added to the end of the package insert. This will be written in layman's terms. It will include information on how the disease is transmitted and the need to continue to employ safer sex practices when using Valtrex suppressively	• Information for Patients will be distributed with each bottle of Valtrex Caplets, including each sample pack • Information for Patients will also be posted on GSK's web site, valtrex.com
Patient Brochure	• Health Care Professionals for provision to patients, with counseling	• A patient friendly brochure that includes information on how genital herpes is transmitted and the need to continue to employ safer sex practices when using Valtrex suppressively for the benefit of reducing transmission.	• GSK sales representatives deliver to Healthcare Professionals and Pharmacists • Available to those who request information by calling GSK

9.4. Closing remarks

In summary, with this Supplemental NDA, GlaxoSmithKline has described clinical trial results that demonstrate that Valtrex 500 mg once daily, when taken by immunocompetent adults as suppressive therapy for recurrent genital herpes and when used in conjunction with safer sex counseling, significantly reduces the risk of genital herpes transmission to an uninfected, immunocompetent, heterosexual, monogamous partner. This reduction in risk of HSV-2 transmission is an additional benefit of suppressive therapy with Valtrex, with no change to drug-associated risks. Therefore, GlaxoSmithKline is submitting this Supplemental NDA to request the addition of information on this new, incremental benefit of suppressive therapy to labeling. In addition, GlaxoSmithKline is proposing plans to build upon an ongoing genital herpes educational program in order to develop and disseminate information that communicates the results from this study with emphasis on the continued importance of safer sex practices when using Valtrex suppressively for the benefit of transmission reduction.

10. REFERENCES

American College of Obstetrics and Gynecologists Practice Bulletin: Management of herpes in pregnancy. *Internat J Gyn Obstet* 2000; 68:165-74.

Adam MB. Effects of condoms on reducing genital herpes transmission (letter). *JAMA* 2001; 286:2095.

Ambinder RF, Burns WH, Lietman PS, et al. Prophylaxis: a strategy to minimise antiviral resistance. *Lancet* 1984; 1:1154-1155.

Anderson JE, Wilson RW, Barker P, et al. Prevalence of sexual and drug related HIV risk behaviors in the US adult population: results of the 1996 national household survey on drug abuse. *J Acquir Immune Defic Syndr* 1999; 21:148-156.

Armstrong G, Schillinger J, Markowitz L, et al. Incidence of herpes simplex virus type 2 infection in the United States. *Am J Epidemiol* 2001; 153:912-20.

Arvin AM, Prober CG. Herpes simplex virus type 2 – a persistent problem. *N Engl J Med* 1997; 337:1158-1159.

Ashley R, Cent A, Maggs V, et al. Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus types 1 and 2. *Ann Int Med* 1999; 115(7):520-526.

Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. *Clin Microbiol Rev* 1999; 12:1-8.

Ashley R, Wald A, Eagleton M. Premarket evaluation of the POCkit HSV-2 type specific serologic test in culture-documented cases of genital herpes simplex virus type 2. *Sex Trans Dis* 2000; 27:266-269.

Ashley RL. Sorting out the new HSV type specific antibody tests. *Sex Trans Inf* 2001; 77:232-237.

Augenbraumn M, Feldman J, Chirgwin K, et al. Increased genital shedding of herpes simplex virus type 2 in HIV seropositive women. *Ann Int Med* 1995; 123:845-847.

Austin, H, Macaluso M, Nahmias A, et al. Correlates of herpes simplex virus seroprevalence among women attending a sexually transmitted disease clinic. *Sex Trans Dis* 1999; 26(6):329-34.

Aymard M. Report on the development of herpes simplex virus antiviral resistance. Unpublished data. 1995.

Bacon TH, Levin MJ, Leary JJ, et al. Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbio Rev* 2003; 16:114-128.

Bagdades EK, Pillay D, Squire SB, et al. Relationship between herpes simplex virus ulceration and CD4+ cell counts in patients with HIV infection. *AIDS* 1992; 6:1317-1320.

Baker DA, Safrin S, Deeter RG, et al. Nine year effectiveness of continuous suppressive therapy with aciclovir in patients with recurrent genital herpes [abstract P220]. In: Program and Abstracts of the Congress of the European Academy of Dermatology and Venerology (Brussels). *J Eur Acad Dermatol Venereol* 1995; 5(suppl 1):S169.

Baker DA, Blythe JG, Miller JM. Once-daily valacyclovir hydrochloride for suppression of recurrent genital herpes. *Obstet Gynecol* 1999; 94:103-106.

Baker D and Hulme L. HSV-2 serologic testing in pregnancy combined with suppressive antiviral therapy for seropositive women is a cost effective strategy for reducing incidence of neonatal herpes in the USA. Infectious Disease Society for Obstetrics and Gynecology, August 2002 (abstract).

Barnabus RV, Carabin H, Garnett GP. The potential role of suppressive therapy for sex partners in the prevention of neonatal herpes: a health economic analysis. *Sex Trans Infect* 2002; 78:425-429.

Barry DW, Lehrman SN, Ellis MN. Clinical and laboratory experience with acyclovir-resistant herpes viruses. *J Antimicrob Chemother* 1986; 18(suppl B):75-84.

Barton S, Davis J, Moss V, et al. Asymptomatic shedding and subsequent transmission of genital herpes simplex virus. *Genitourin Med* 1987; 63:102-105.

Barton S, Munday P, Patel R. Asymptomatic shedding of herpes simplex virus from the genital tract: uncertainty and its consequences for patient management. *Int J STD AIDS* 1996; 7:229-232.

Benedetti J, Zeh J, Selke S, et al. Frequency and reactivation on nongenital lesions among patients with genital herpes simplex virus. *Am J Med* 1995; 98:237-242.

Benedetti JK, Zeh J and Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Int Med* 1999; 131:14-20.

Blower SM, Porco TC, Darby G. Predicting and preventing the emergence of antiviral drug resistance in HSV-2. *Nat Med* 1998; 4:664-665.

Breinig MK, Kingsley LA, et al. Epidemiology of genital herpes in Pittsburgh: serologic, sexual, and racial correlates of apparent and inapparent herpes simplex infections. *J Infect Dis* 1990; 162(2):299-305

Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. *N Engl J Med* 1987; 317:1246-51.

Brown ZA, Benedetti JK, Watts DH, et al. A comparison between detailed and simple histories in the diagnosis of genital herpes complicating pregnancy. *Am J Obstet Gynecol* 1995; 172:1299-1303.

Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997; 337:509-15.

Brown ZA. Genital herpes complicating pregnancy. *Dermatologic Clinics* 1997; 16:805-809.

Brown ZA, Wald A, Ashley Morrow R, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003; 289:203-209.

Brugha R, Keersmaekers K, Renton A, et al. Genital herpes infection: a review. *Int J Epidemiol* 1997; 26(4):698-709.

Bryson Y, Dillon M, Bernstein D, et al. Risk of acquisition of genital herpes simplex virus type 2 in sex partners of persons with genital herpes: a prospective couple study. *J Inf Dis* 1993; 167:942-946.

Buchacz K, McFarland W, Hernandez M, et al. Prevalence and correlates of herpes simplex virus type 2 infection in a population-based survey of young women in low-income neighborhoods of northern California. *Sex Transm Dis* 2000; 27:393-400.

Buimovici-Klein E, Lange M, Ong KR, et al. Virus isolation and immune studies in a cohort of homosexually active men. *J Med Virol* 1988; 25:371-85.

Butler T, Donovan B, Taylor J, et al. Herpes simplex virus type 2 in prisoners, New South Wales, Australia. *Int J STD AIDS* 2000; 11(11):743-7.

Cameron DW, Simonsen JN, D'Costa LJ, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989; 2(8660):403-7.

Carney O, Ross E, Ikkos G, et al. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. *Genitourin Med* 1993; 69:457-459.

Carney O, Ross E, Bunker C, et al. A prospective study of the psychological impact on patients with a first episode of genital herpes. *Genitourin Med* 1994; 70:40-45.

Casper C and Wald A. Condom use and the prevention of genital herpes acquisition. *Herpes* 2002; 9(1):10-4.

Cates W. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. *Sex Transm Dis* 1999; 26 (suppl); S2-S7.

Catania J, Coates T, Stall R, et al. Prevalence of AIDS-related risk factors and condom use in the United States. *Science* 1992; 258:1101-1106.

Catania JA, Binson D, Dolcini MM, et al. Risk factors for HIV and other sexually transmitted diseases and prevention practices among US heterosexual adults: changes from 1990 to 1992. *Am J Public Health* 1995; 85:1492-1499.

Catotti DN, Clarke P, Catoe KE. Herpes revisited: still a cause of concern. *Sex Transm Dis* 1993; 20:77-80.

Centers for Disease Control and Prevention. Tracking the Hidden Epidemics: Trends in STDs in the United States. 2000.

Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *Morbid Mortal Wkly Rep* May 10, 2002; Volume 51 (No. RR-6).

Chatis PA, Miller CH, Schrager LE, et al. Successful treatment with foscarnet of an acyclovir resistant mucocutaneous infection with herpes simplex virus in a patient with acquired immunodeficiency syndrome. *N Engl J Med* 1989; 320:297–300.

Christophers J, Clayton J, Craske J, et al. Survey of resistance of herpes simplex virus to acyclovir in Northwest England. *Antimicrob Ag Chemother* 1998; 42:868-872.

Coen DM, Shaeffer PA. Two distinct loci confer resistance to acycloguanosine in herpes simplex virus type 1. *Proc Natl Acad Sci USA* 1980; 77:2265-2269.

Coen DM. Acyclovir-resistant, pathogenic herpesviruses. *Trends Microbiol* 1994; 2:481-485.

Collins P. Analysis of a TK-deficient herpes simplex virus from a patient in the 1980s which is able to reactivate in the mouse model and may have compensatory mutations elsewhere in the HSV genome. Personal communication / GSK data on file.

Collins P, Darby G. Laboratory studies of herpes simplex virus strains resistant to acyclovir. *Rev Med Virol* 1991; 1:19–28.

Conant MA, Schacker T, Murphy RL, et al. Valciclovir versus aciclovir for herpes simplex virus infection in HIV infected individuals-two randomised trials. *Int J STD AIDS* 2002; 13:12-21.

Corey L, Adams HG, Brown ZA, et al. Genital herpes simplex virus infections: clinical manifestations, course and complications. *Ann Int Med* 1983a; 98(6):958-972.

Corey L, Fife KH, Benedetti JK, et al. Intravenous acyclovir for the treatment of primary genital herpes. *Ann Intern Med* 1983b; 98(6):914-21.

Corey L. Herpes simplex virus infections during the decade since the licensure of acyclovir. *J Med Virol* 1993; suppl(1):7-12.

Corey L. The current trend in genital herpes. Progress in prevention. *Sex Transm Dis* 1994; 21:S38-S44.

Corey L, Langenberg AGM, Ashley R. Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection: two randomized controlled trials. *JAMA* 1999a; 282(4):331-340.

Corey L and Wald A. Genital herpes. In: Holmes KK, Mardh PA, Sparling PF, eds. *Sexually Transmitted Diseases.* 3rd ed. New York, NY: McGraw Hill; 1999b:285-312.

Corey L and Handsfield HH. Genital herpes and public health: Addressing a global problem. *JAMA* 2000; 282(6):791-794.

Corey L, Tyring S, Sacks S, et al. Once daily valacyclovir reduces transmission of genital herpes. In: Proceedings from the Interscience Conference on Antimicrobial Agents and Chemotherapy, 2002, San Diego, CA (Abstract).

Cowan FM, Johnson AM, Mindel A. Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals [letter]. *J Infect Dis* 1993; 167:772.

Cowan FM, Johnson AM, Ashley R, et al. Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Inf Dis* 1996;174:470-475.

Cox DR. A simple example of a comparison involving qualtal data. *Biometrika* 1966; 53:215-220.

Crumpacker CS, Schnipper LE, Marlowe SI, et al. Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. *N Engl J Med* 1982; 306:343-346.

Diamond C, Selke S, Ashley R, et al. Clinical course of patients with serological evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. *Sex Transm Dis* 1999; 26:221-225.

Diaz-Mitoma F, Ruben M, Sacks S, McPherson P, Caisse G. Detection of viral DNA to evaluate outcome of antiviral treatment of patients with recurrent genital herpes. *J Clin Microbiol* 1996; 34:657-663.

Dickerson MC, Johnston J, Delea TE, et al. The causal role for genital ulcers disease as a risk factor for transmission of human immunodeficiency virus: an application of the Bradford Hill criteria. *Sex Transm Dis* 1996; 23:429-440.

Dobbins, JG, Mastro TD, Nopkesorn T, et al. Herpes in the time of AIDS: a comparison of the epidemiology of HIV-1 and HSV-2 in young men in northern Thailand. *Sex Transm Dis* 1999; 26(2):67-74.

Erlich KS, Millis J, Chatis P, et al. Acyclovir-resistant herpes simplex virus infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989; 320:293-292.

Elion GB, Furman PA, Fyfe JA, et al. Selectivity of action of an antiherpetic agent, 9-(2-hydroxyethoxymethyl) guanine. *Proc Natl Acad Sci USA* 1977; 79:5716-5720.

Elion GB. Acyclovir: discovery, mechanism of action and selectivity. *J Med Virol* 1993; Suppl 1: 2-6.

Englund JA, Zimmerman ME, Swierkosz EM, et al. Herpes simplex virus resistant to acyclovir: a study in a tertiary care center. *Ann Intern Med* 1990; 112:416-422.

Enzensberger R, Braun W, Huly C, et al. Prevalence of antibodies to human immunodeficiency virus (HIV) infection. *Infection* 1991; 19:140-145.

Feinberg JE, Hurwitz S, Cooper D, et al. A randomized, double-blind trial of valacyclovir prophylaxis for cytomegalovirus disease with patients with advanced human immunodeficiency virus infection. *J Inf Dis* 1998; 177:48-56.

Fife KH, Crumpacker CS, Mertz GJ, et al. Recurrence and resistance patterns of herpes simplex virus following cessation of ≥6 years of chronic suppression of acyclovir. *J Inf Dis* 1994; 169:1338-1341.

Field H. Herpes simplex virus and antiviral drug resistance-current trends and future prospects. *J Clin Virol* 2001; 21:261-269.

Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *New Engl J Med* 1997; 337:1105-1111.

Food and Drug Administration: Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998

Gart J. Point and interval estimation of the common odds ratio in the combination of 2x2 contingency tables. *Biometrica* 1970; 57:471-5.

Gaudreau A, Hill E, Balfour HH Jr, et al. Phenotypic and genotypic characterization of acyclovir-resistant herpes simplex viruses from immunocompromised patients. *J Infect Dis* 1998; 178:297–303.

Gershengorn HB, Blower SM. The impact of antivirals and the emergence of drug resistance: HSV-2 epidemic control. *AIDS Patient Care STDs* 2000; 14:133-142.

Gershengorn HB, Darby G, Blower SM. Predicting the emergence of drug-resistant HSV-2: new predictions. *BioMed Central Infectious Diseases* 2003, in press.

Gilbert LK, Schulz SL, Ebel C. Education and counseling for genital herpes: perspectives from patients. *Herpes* 2002; 9:20-24.

GlaxoSmithKline Document RM1999/00357/00. A cross-sectional surveillance study of a TMA-like syndrome in HIV-infected patients in the CHORUS observational database. 1999.

GlaxoSmithKline Document BQRT/96/0001. Final Study Report for Protocol 123-026: A comparative trial of valaciclovir with aciclovir and placebo for the suppression of recurrent genital herpes infections in immunocompetent patients. 1996.

GlaxoSmithKline Document RM2002/00028/00. Final Study Report for Protocol HS230018: An international, randomized, double-blind, placebo-controlled study of valaciclovir for the suppression of recurrent ano-genital HSV infections in HIV-infected subjects. 2002.

Gnann JW, Clark FM, Hodges-Savola CA, et al. Acyclovir-resistant herpes simplex virus in HSV-infected individuals: results from an ongoing US surveillance study. *Antiviral Res* 1999; 41:Abstract 86, A59.

Gold, J. The Albion Street Centre Database, Sydney, Australia. *J Acquir Imm Defic Syndr and Hum Retrovir* 1998; 17(suppl 1):S34-S37.

Golden MP, Kim S, Hammer SM, et al. Activation of human immunodeficiency virus by herpes simplex virus. *J Inf Dis* 1992; 166:494-499.

Grey F, Sowa M, Collins P, et al. Characterisation of a neurovirulent aciclovir resistant variant of herpes simplex virus. *J Gen Virol* 2003, in press.

Griffiths PD. Studies to define viral cofactors for human immunodeficiency virus. *Infect Agents Dis* 1992; 1:237-244.

Handsfield HH, Stone KM, Wasserheit J. Prevention agenda for genital herpes. *Sex Transm Dis* 1999; 26**:**228–231.

Handsfield H. Public health strategies to prevent genital herpes: where do we stand? *Current Infec Dis Reports* 2000; 2:25-30.

Handsfield HH. Genital herpes. 2001. McGraw-Hill.

Heng MCY, Heng SY, Allen SG. Co-infection and synergy of human immunodeficiency virus-1. *Lancet* 1994; 343:255-258.

Hill J. *In vitro* acyclovir sensitivity monitoring: pre-ACV and six-year suppression results. GlaxoSmithKline document # TGZZ/93/0008. 1993.

Hill EL, McClernon DR, Collins P, et al. Herpes simplex virus sensitivity to acyclovir: two decades of in vitro results. Eleventh International Meeting of the Society for STD Research. New Orleans, Louisiana. August 1995; # 187.

Hodinka R, Swierkosz E, Lancaster D, et al. Antiviral susceptibility testing; proposed standard. 2000. M33-P, i-34. National Committee for Clinical Laboratory Standards. Wayne, PA, 19087–1898, USA.

Holmberg SD, Gerber AR, Stewart JA, et al. Herpes simplex virus type 2 and HIV seroconversion [letter]. *J Acquir Imm Defic Syndr* 1991;4:732-4.

Hook E, Connon RO, Nahmias AJ. Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals. *J Inf Dis* 1992; 165:251-255.

Horsburgh BC, Chen S-H, Hu A, et al. Recurrent acyclovir-resistant HSV infection in an immunocompromised patient: can strain differences compensate for loss of thymidine kinase in pathogenesis? *J Inf Dis* 1998; 178:618-625.

Huerta K, Berkelhamer S, Klein J, et al. Epidemiology of herpes simplex virus type 2 infections in a high-risk adolescent population. *J Adolesc Health* 1996; 18(6):384-6.

Hwang CB, Horsburgh BC, Pelosi E et al. A net +1 frameshift permits synthesis of thymidine kinase from a drug-resistant herpes simplex virus mutant. *Proc Natl Acad Sci USA* 1994, 91:5461-5465.

Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Inf Dis* 1998; 178:349-359.

Johnson RE, Nahmias AJ, Magder et al. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* 1989; 321:7-12.

Jones TJ, Paul R. Disseminated acyclovir-resistant herpes simplex virus type 2 treated successfully with foscarnet. *J Infect Dis* 1995; 121:508–509.

Kimberlin DW and Whitley RJ. Antiviral resistance: mechanisms, clinical significance, and future implications. *J Antimicro Chemo* 1996; 37:403-421.

Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatr* 2001a; 108:230-8 a.

Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatr* 2001b; 108:223-9 b.

Kinghorn, GR. Epidemiology of genital herpes. *J Int Med Res* 994**;** 22(Suppl 1):14A-23A.

Koelle D, Wald A. Herpes simplex virus: the importance of asymptomatic shedding. *J Antimicrobiol Chem* 2000; 45:Topic T3, 1-8.

Kost RG, Hill EL, Tigges M, et al. Brief report: recurrent acyclovir-resistant genital herpes in an immunocompetent patient. *N Engl J Med* 1993; 329: 1777-1782.

Koutsky L, Stevens CE, Holmes KK, et al. Underdiagnosis of genital herpes by current clinical and viral-isolation procedures. *N Engl J Med* 1992; 326:1533-1539.

Kulhanjian JA, Soroush V, Au DS, et al. Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy. *N Engl J Med* 1992; 326:916-20.

Lafferty WE, Coombs RW, Benedetti J, et al. Recurrences after oral and genital herpes simplex virus infection: influence of anatomic site and viral type. *N Engl J Med* 1987; 316:1444-1449.

Lafferty WE, Downey L, Celum C, et.al. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* 2000; 181:1454-1457.

Lalezari JP, Drew WL, Glutzer E, et al. Treatment with intravenous (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl] cytosine of acyclovir-resistant mucutaneous infection with herpes simplex virus in a patient with AIDS. *J Infect Dis* 1994; 170:570–572.

Lalezari J, Schacker T, Feinberg J, et al. A randomized, double-blind, placebo-controlled trial of cidofivir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Inf Dis* 1997; 176:892-898.

Langenberg A, Benedetti J, Jenkins J et al. Development of clinically recognizable genital lesions among women previously identified as having "asymptomatic" herpes simplex virus type 2 infections. *Ann Int Med* 1989; 110(11):882-887.

Langenberg AG, Corey L, Ashley RL, et.al. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron Vaccine Study Group. *N Engl J Med* 1999; 341(19):1432-1438.

Latkin, CA, Vlahov D, et al. Socially desirable responding and self-reported HIV infection risk behaviors among intravenous drug users. *Addiction* 1993; 88(4):517-526.

Latkin, CA and Vlahov D. Socially desirable response tendency as a correlate of accuracy of self-reported HIV serostatus for HIV seropositive injection drug users. *Addiction* 1998; 93(8):1191-1197.

Laumann, EO, Gagnon JH, et al. Sexual networks: the social organization of sexuality. 1994. Chicago, University of Chicago Press: pp 225-268.

Lehrman SN, Douglas JM, Corey L, Barry DW. Recurrent genital herpes and suppressive oral acyclovir therapy: relation between clinical outcome and *in-vitro* drug sensitivity. *Ann Int Med* 1986; 104:786-790.

Lipsitch M, Bacon TH, Leary JJ, Antia R, and Levin BR. Effects of antiviral usage on transmission dynamics of herpes simplex virus type 1 and on antiviral resistance: predictions of mathematical models. *Antimicrob Agents and Chemother* 2000; 44: 2824-2835.

Lowance D, Nuemayer HH, Legendre CM, et al. Valacyclovir for the Prevention of Cytomegalovirus Disease after Renal Transplantation. *NEJM* 1999; 340:1462-1469.

Lowhagen, GB, Tunback P, Andersson K, et al. Recurrent genital herpes in a population attending a clinic for sexually transmitted diseases. *Acta Derm Venereol* 2001; 81(1):35-37.

Mann SL, Meyers JD, Holmes KL, Corey L. Prevalence and incidence of herpesvirus infections among homosexually active men. *J Inf Dis* 1984; 149(6):1026-1027.

Marques AR, Straus SE. Herpes simplex type 2 infections: an update. *Disease A-Month* 2000; 46:327-359.

Mascola JR. Herpes simples virus vaccines – why don't antibodies protect? *JAMA* 1999; 282(4):379-380.

McLaren C, Ellis MN, Hunter GA. A colorimeteric assay for the measurement of the sensitivity of herpes simplex viruses to antiviral agents. *Antiviral Res* 1983; 3:223–234.

McLaren C, Corey L, Dekket C, Barry DW. *In vitro* sensitivity to acyclovir in genital herpes simplex viruses from acyclovir-treated patients. *J Inf Dis* 1993; 148:868-875.

Mertz GJ, Schmidt O, Jourden JL, et. al. Frequency of acquisition of first episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Trans Dis* 1985; 12:33-9.

Mertz GJ, Coombs RW, Ashley RL, et al. Transmission of genital herpes in couples with one symptomatic and one asymptomatic partner: a prospective study. *J Infect Dis* 1988; 157:1169-1177.

Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med* 1988; 85:14-19.

Mertz GJ, Benedetti J, Ashley R, Selke S, Corey L. Risk factors for sexual transmission of genital herpes. *Ann Intern Med* 1992; 116:197-202.

Mertz, GJ. Epidemiology of genital herpes infections. *Infect Dis Clin North Am* 1993; **7**(4):825-39.

Mindel A. Long-term clinical and psychological management of genital herpes. *J Med Virol* 1993; (suppl 1):39-44.

Mindel A. Psychological and psychosexual implications of herpes simplex virus infections. *Scand J Infect Dis* 1996; suppl 100:27-32.

Mole L, Ripich S, Margolis D, et al. The impact of active herpes simplex virus infection on human immunodeficiency virus load. *J Inf Dis* 1997; 176:766-770.

Moore RD. Schistocytosis and a thrombotic microangiopathy-like syndrome in hospitalized HIV-infected patients. *Am J of Hematology* 1999; 60:116-120.

National Institutes of Health Report: Scientific evidence on condom effectiveness for sexually transmitted disease (STD) prevention. Herdon, VA, USA. 2001.

Nugier F, Colin JN, Aymard J, et al. Occurrence and characterization of acyclovir-resistant herpes simplex virus isolates: report on a two-year sensitivity screening survey. *J Med Virol* 1992; 36:1-12.

Oberle, MW, Rosero-Bixby L, et al. Herpes simplex virus type 2 antibodies: high prevalence in monogamous women in Costa Rica. *Am J Trop Med Hyg* 1989; 41(2): 224-229.

O'Brien, FP. Work-related fear of AIDS and social-desirability response bias. *Psychol Rep* 1989; 65(2):371-378.

Overall JC. Herpes simplex virus infection of the fetus and newborn. *Pediatric Annals* 1994; 23:131-136.

Patel R, Delehanty J, et al. Valaciclovir for the treatment of first episode genital herpes. Presented at the 1st European Congress on Chemotherapy, May 1996, Glasgow, UK. Abstract W116.

Patel R, Bodsworth N, Woolley P, et al. Valacyclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once-daily therapy. *Genitourin Med* 1997a; 73:105-109.

Patel R, Cowan F, Barton S. Advising patients with genital herpes. *Brit Med J* 1997b; 314:85-86.

Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet* 2002; 359:1686-1689.

Posavad C, Koelle D, Shaughnessy M, Corey, L. Severe genital herpes infections in HIV-infected individuals with impaired herpes simplex virus-specific CD8+ cytotoxic T lymphocyte responses. *Proc. Natl. Acad. Sci*. 1997; 94:10289-10294.

Reiff-Elridge R, Heffner CR, Ephross SA, et al. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol* 2000; 182:159-63.

Reitano M, Stern J, et.al. Genital herpes: a patient guide to treatment. American Medical Association 1997.

Reitano R, Tyring S, Lang W, et al. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale, dose-range-finding study. *J Inf Dis* 1998; 178:603-610.

Reyes M, Graber JM, Wetherall N, et.al. Acyclovir-resistant herpes simplex virus: preliminary results from a national surveillance system. *Arch Int Med* 2003 (in press).

Romano L, Venturi G, Vivarelli A, et al. Detection of a drug-resistant human immunodeficiency virus varient in a newly infected heterosexual couple. *Clin Infect Dis* 2002, 34:116-117.

Rooney J, Felser J, Ostrove J, Strauss S. Acquisition of genital herpes from an asymptomatic sexual partner. *N Engl J Med* 1986; 314:1561-1564.

Rosenthal SL, Stanberry LR, et al. Seroprevalence of herpes simplex virus types 1 and 2 and cytomegalovirus in adolescents. *Clin Infect Dis* 1997; 24(2):135-9.

Sacks SL, Safrin SD. BID famciclovir (FCV) suppression of asymptomatic (Asx) genital herpes simplex virus (HSV) shedding in men. In: Proceedings of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, California, 24-27 September, 1998. American Society for Microbiology, Washington DC, USA, 1998: Abstr H-12.

Safrin S, Crumpacker C, Chatis P, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. *N Engl J Med* 1991; 325:551–555.

Safrin S, Elbeik T, Phan L, et al. Correlation between response to acyclovir and foscarnet therapy and *in vitro* susceptibility results for isolates of herpes simplex virus from immunodeficiency-infected patients. *Antimicrob Agents Chemother* 1994; 38:1246–1250.

Sarisky RT, Bacon T, Boon R, et al. Penciclovir susceptibilities of herpes simplex virus isolates from patients using penciclovir cream for treatment of recurrent herpes labialis. *Antimicrob Agents Chemoth* 2002; 46:2848-2853.

Schacker T, Zeh J, Hu HL, et al. Frequency of symptomatic and asymptomatic HSV-2 Reactivations. *J Inf Dis* 1998; 178:1616-22.

Scott LL, Alexander J. Cost-effectiveness of acyclovir suppression to prevent recurrent genital herpes in term pregnancy. *Amer J Perinatol* 1998; 15:57-62.

Scott LL, Hollier D, McIntire D, et al. Acyclovir suppression to prevent recurrent genital herpes at delivery. *Infect Dis Obstet Gynecol* 2002; 10:71-77.

Severson, J and Tyring S. Relationship between herpes simplex viruses and human immunodeficiency virus infection. *Arch Dermatol* 1999; 135:1393-1397.

Shuster JJ. Fixing the number of events in large comparative trials with low event rates: a binomial approach. *Controlled Clinical Trials* 1993; 14:198-208.

Siegel D, Golden E, Washington AE, et al. Prevalence and correlates of herpes simplex infections. The population-based AIDS in Multiethnic Neighborhoods Study. *JAMA* 1992; 268(13):1702-8.

Smith, JS, Herrero R, Munoz N, et al. Prevalence and risk factors for herpes simplex virus type 2 infection among middle-age women in Brazil and the Philippines. *Sex Transm Dis* 2001; 28(4):187-94.

Snoeck R, Andrei G, Gerard M, et al. Successful treatment of progressive mucocutaneous infection due to acyclovir and foscarnet-resistant herpes simplex virus

with (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine (HPMPC). *Clin Infect Dis* 1994; 18:570–578.

Stamm WE, Handsfield HH, Romaplo AM, et al. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA* 1988; 260:1429-33.

Stanberry LR, Myers MG, Stephanopoulos DE, et al. Preinfection prophylaxis with herpes simplex virus glycoprotein immunogens: factors influencing efficacy. *J Gen Virol* 1989; 70(12):3177-3185.

Stanberry LR, Cunningham AL, Mindel A, et al. Prospects for control of herpes simplex virus disease through immunization. *Clin Infect Dis* 2000; 30:549-566.

Stanberry LR, Spruance SL, Cunningham AL, et al. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. *N Eng J Med* 2002; 347 (21):1652-1661.

Straus S, Rooney J, Hallahan C. Acyclovir suppresses subclinical shedding of herpes sinplex virus. *Ann Intern Med* 1996; 125:776-777.

Sucato GC, Celum C, Dithmer D, et al. Demographic rather than behavioral risk factors predict herpes simplex virus type 2 infection in sexually active adolescents. *Pediatr Infect Dis J* 2001; 20(4):422-6.

Swetter SM, Hill EL, Kern ER, et al. Chronic vulvar ulceration in an immunocompetent woman due to acyclovir-resistant, thymidine kinase-deficient herpes simplex virus. *J Inf Dis* 1998; 177:543-550.

Tyring SK, Baker DA, Snowden W. Valacyclovir for herpes simplex infection: long-term safety and sustained efficacy after 20 years' experience with aciclovir. *J Infect Dis* 2002; 186(Suppl 1):S40-46.

Wade JC, McLaren C, Meyers JD. Frequency and significance of acyclovir-resistant herpes simplex virus isolated from marrow transplant patients receiving multiple courses of treatment with acyclovir. *J Infect Dis* 1983; 148:1077–1082.

Wald A, Zeh J, Selke S, et al. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995; 333:770-75.

Wald A, Zeh J, Barnum G, et al. Suppression of asymptomatic shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996; 124:8-15.

Wald A, Corey L, Cone R, et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women: effect of acyclovir treatment. *J Clin Invest* 1997a; 99:1092-1097.

Wald A, Koutsky L, Link K, et al. Genital herpes in a primary care clinic. Demographic and sexual correlates of herpes simplex type 2 infections. *Sex Transm Dis* 1997b; 24(3):149-55.

Wald A, Warren T, Hu H et.al. Suppression of asymptomatic shedding of herpes simplex virus type 2 in the genital tract with valacyclovir. In: Proceedings of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, California, 24-27 September, 1998. American Society for Microbiology, Washington DC, USA, 1998: Abstr H-82.

Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000; 342(12):844-850.

Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA* 2001; 285:3100-3106.

Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Inf Dis* 2002a; 185:45-52.

Wald A, Zeh J, Selke S, et al. Genital shedding of herpes simplex virus among men. *J Infect Dis* 2002b; 186:S34-S39.

Watts H. et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for reduction of herpes simplex virus shedding and cesarean section. *Am J Obstet Gynecol* 2003 (in press).

Weller S, Blum MR, Doucette M, et al. Pharmacokinetics of the acyclovir pro-drug valacyclovir after escalating single- and multiple-dose administration to normal volunteers. *Clin Pharmacol Ther* 1993; 54:595-605.

White PJ and Garnett GP. Use of antiviral resistance treatment and prophylaxis is unlikely to have a major impact on the prevalence of herpes simplex virus type 2. *Sex Trans Inf* 1999; 75:49-54.

Whitley RJ, Arvin A, Prober CG, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *N Engl J Med* 1991; 324:444-449.

Whitley R and Roizman B. Herpes simplex viruses: is a vaccine tenable? *J Clin Invest* 2002; 110:145-151.

UNAIDS/WHO Epidemiological Fact Sheet on HIV/AIDS and Sexually Transmitted Infection: United States of America; 2002 Update.

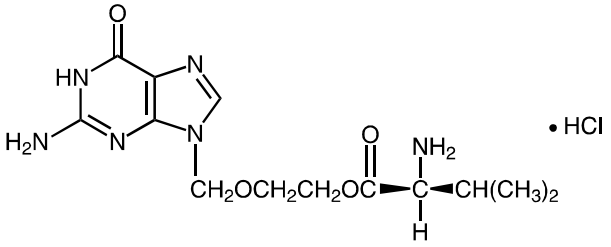
US National Center for Health Statistics. CD-ROM, 1990 National Hospital Discharge Survey, series 13 No. 1.

Zelen M. The analysis of several 2x2 contingency tables. *Biometrika* 1971; 58(1):129-137.

APPENDIX 1. MECHANISM OF ACTION AND APPROVED INDICATIONS FOR VALTREX

1. Mechanism of action of valacyclovir

Valtrex (valacyclovir hydrochloride) is the hydrochloride salt of *L*-valyl ester of the antiviral drug acyclovir (Zovirax brand, GlaxoSmithKline). The discovery of valacyclovir is the result of an extensive program aimed at the synthesis and development of a new antiviral drug that provides significantly higher oral acyclovir bioavailability. Valtrex Caplets are for oral administration. The chemical name of valacyclovir hydrochloride is *L*-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester, monohydrochloride. It has the following structural formula:



After oral administration, valacyclovir is rapidly and almost completely converted to acyclovir and L-valine, a naturally occurring amino acid. Conversion of valacyclovir to acyclovir is by first-pass hepatic and intestinal metabolism. An enzyme isolated from human liver referred to as valacyclovir hydrolase probably mediates this conversion.

Acyclovir is a synthetic purine nucleoside analogue with highly selective *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including HSV-1, HSV-2, varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV, VZV and EBV (in the case of CMV, this process is mediated by a protein kinase encoded by the UL97 gene). This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to other herpesviruses is due to its more efficient phosphorylation by the viral TK.

Valacyclovir achieves high bioavailability of acyclovir, 3- to 5-fold higher than achieved with oral acyclovir [Weller 1993]. Plasma exposures of acyclovir following oral valacyclovir approach those found after intravenous acyclovir. In comparison to acyclovir, this improved oral bioavailability enabled valacyclovir to achieve once or twice daily dosing for the management of genital herpes infections, without compromising acyclovir's exceptional safety profile.

2. Approved indications for Valtrex in the US

A summary of approved indications and doses for Valtrex, along with the approval dates for each, is provided in Table 35.

Table 35. Approved Indications for Valtrex in the US

Indication	Dosage	Approval Date
Treatment of herpes zoster	1 g three times daily x 7 days	June 23, 1995
Treatment of recurrent genital herpes in immunocompetent adults	500 mg twice daily x 3 days	December 15, 1995
Treatment of initial episodes of genital herpes in immunocompetent adults	1 g twice daily x 10 days	October 4, 1996
Suppression of recurrent genital herpes in immunocompetent adults	1 g once daily (>9 recurrences/year) OR 500 mg once daily (≤9 recurrences/year)	September 26, 1997
Treatment of herpes labialis (cold sores) in immunocompetent adults	2 g twice daily x 1 day	September 13, 2002
Suppression of recurrent genital herpes in HIV-infected individuals	500 mg twice daily	April 1, 2003

[1] Initially approved as a 5-day regimen (500 mg BID x 5 days)

APPENDIX 2. REVIEW OF KEY FACTORS ASSOCIATED WITH HSV-2 TRANSMISSION OR ACQUISITION

1. Female gender

A number of studies have examined the role gender may play in the risk of transmission and acquisition of HSV-2. These studies have consistently identified female gender as being associated with a higher risk for acquiring HSV-2 infection [Johnson 1989; Huerta 1996; Fleming 1997; Rosenthal 1997]. In a prospective study of 144 heterosexual, HSV-2-discordant couples to evaluate the rate and risk of HSV-2 transmission, 11 of the 14 acquisitions (79%) noted during the study period occurred in women [Mertz 1992]. In a large study of 515 monogamous couples to evaluate an ineffective experimental HSV-2 vaccine, 21 of 28 acquisitions (75%) observed on study were in females who had HSV-2 infected male source partners [Corey 1999a]. Univariate analysis determined that women in this study were over five times as likely to acquire HSV-2 than men (HR=5.51; 95% CI: 2.12-14.4). The acquisition rate per 10,000 sexual acts was 8.9 for women compared to 1.5 for men ($p<0.001$) [Wald 2001]. In an analysis of this study combined with a second study of the same vaccine, a relative risk of HSV-2 acquisition of 0.65 for males (95% CI, 0.46-0.93, $P = 0.02$) was calculated, providing additional data supporting the increased susceptibility of women to HSV-2 acquisition.

In another study, four of thirteen women in steady relationships with HSV-2 positive men seroconverted over three years, compared with no seroconversions among 16 seronegative men with HSV-2 positive female partners [Bryson 1993]. In a study of adolescents, HSV-2 seropositivity was significantly higher in females than in males (OR=6.0; 95% CI: 2.3-15.9), with a seroprevalence of 17% and 4%, respectively [Sucato 2001]. The youngest girls were more likely to be HSV-2-seropositive than young boys, despite similar numbers of sexual partners and condom use. None of the boys 16 years old or younger were seropositive for HSV-2, but 19% of girls 16 years old or younger were seropositive.

Potential reasons for greater susceptibility to HSV-2 acquisition in women include anatomical differences (e.g., differences in the genital epithelium, larger muscosal surface area), longer exposure to inoculum, and a higher rate of viral reactivation and disease recurrences among men than women. In adolescents, the difference in gender-specific infection rates might be attributable in part to differences in partner selection, as adolescent girls are more likely than adolescent boys to have older sexual partners who are more likely to be HSV-2-seropositive than younger men [Laumann 1994; Fleming 1997; Sucato 2001].

2. Use of condoms

Several studies have been published comparing behaviors reported by HSV-2 seropositive vs HSV-2 seronegative participants, including the use of condoms. However, almost all published studies on condoms and HSV-2 infection have been retrospective or cross-sectional, i.e., designs which prevent a definitive establishment of the temporal relationship between the use of condoms and HSV-2 acquisition. Other

biases also play a role in distorting what may be the true relationship between condom use and HSV-2 acquisition. Participants enrolled in a study of HSV acquisition may incorrectly report their use of condoms, either because they may not remember correctly or because they were trying to please the investigators. This bias is evident when biological endpoints of STD detection do not always correlate with reported history of condom use [O'Brien 1989; Latkin 1993; Latkin 1998]. Despite these limitations, several studies of condom use and HSV-2 acquisition have been completed over the past decade. The most compelling data can be gained from the analysis carried out by Wald et al using results from a large, controlled trial of an ineffective HSV-2 vaccine candidate [Wald 2001]; these analyses have been previously described in Section 2.4.3.1 of this Briefing Document. In this section, reviews of other published studies are provided. Not unexpectedly, these studies support difference conclusions depending on the population included in the study and do not necessarily deliver a consistent message with respect to condom efficacy in preventing HSV-2 transmission.

In a study of women attending an STD clinic in Alabama, participants were asked about their use of barrier contraception during vaginal sex within the month prior to interview. Women categorized as 'consistent' vs 'inconsistent' users had similar rates of HSV-2 seroprevalence of 64% and 66%, respectively [Austin 1999]. Over 60% of the study participants in both groups had a history of genital warts, gonorrhoea, syphilis, chlamydia, or trichomoniasis. These results indicate that retrospective accounts of condom use in the month prior to study entry are not a sufficient marker of risk for a chronic viral infection. In a more recent study from a Swedish STD clinic, condom use among HSV-2-positive individuals did not lead to a lower seroprevalence of HSV-2 among their partners, though no numbers were given [Lowhagen 2001]. In a study of adolescents detained in a juvenile detention facility in California, no significant difference in HSV-2 prevalence was found based on whether they reported using condoms with ≥50% of sexual encounters or ≤50% of sexual encounters [Huerta 1996].

Three international studies have reported an increase in HSV-2 seroprevalence with the use of condoms. In a study of Filipino women, participants who were HSV-2 seropositive were more likely to report ever using condoms (odds ratio [OR] = 2.7; 95% confidence interval [CI]: 0.8-9.4), although this finding was not statistically significant [Smith 2001]. Of interest were the low HSV-2 seroprevalence among Filipino women (9%) and the absence of 'high risk' sexual behavior in the Philippines; 90% of Filipino women reported having only one lifetime sexual partner. Young male conscripts entering the army in Thailand were found to have an HSV-2 seroprevalence of 14.9%. The seroprevalence of HSV-2 was higher among men who reported having had sex with a female sex worker, at 18.2%. Higher HSV-2 seroprevalence was found in those who used condoms versus men who never used condoms, suggesting that perhaps these men modified their sexual behavior according to the degree of perceived risk of STD acquisition [Dobbins 1999]. In a study of female prisoners in Australia with an HSV-2 seroprevalence of 58%, those who reported using condoms occasionally or never were less likely to be HSV-2 seropositive in univariate analysis (OR = 0.3; 95% CI: 0.1-0.9) [Butler 2000]. Additionally, female prisoners were more likely to use condoms if they did not report a stable partner, leading the authors to speculate that condom use may have been an indication of choosing higher risk sexual partners. The association between condom use and HSV-2 infection was not seen in male prisoners.

Other studies have reported lower HSV-2 seroprevalence among individuals who used condoms more frequently. A study among women attending a primary care clinic in Seattle reported women who used condoms with 0-10% of their partners were more likely to be HSV-2 seropositive when compared with woman who used condoms with 91-100% of their partners (OR = 4.6; 95 % CI: 1.0-10.7) [Wald 1997b]. This finding was associated only with condom use by percentage of partners, not by percentage of sexual encounters. However, women with multiple partners were less likely to report condom use, suggesting that the observed effect of condoms is relative to the degree of sexual activity and exposure to HSV-2, rather than condom use per se. No association between reported condom use and HSV-2 seroprevalence was noted among men. In a study of male and female adolescents aged 14-19 years in Seattle, participants who were HSV-2 seropositive were more likely to report not using a condom with their last sexual encounter than those who were HSV-2 seronegative (OR=1.5; 95 % CI: 0.7-3.3), although this finding was not statistically significant [Sucato 2001]. In a study among heterosexual couples in Seattle and New Mexico, where one partner was infected with HSV-2 and not taking suppressive antiviral therapy, the annual rate of infection in couples reporting the use of barrier methods of contraception was reported as nearly one-third of that of couples who did not use such methods (5.7% versus 13.6%), although this finding was not statistically significant [Mertz 1992]. A small study from Los Angeles followed 29 HSV-2 serodiscordant couples for a mean of 16 months and documented four seroconversions. All seroconverters were women; none used condoms during times when the source partner was asymptomatic. A study of women in Brazil reported that those who were HSV-2 seropositive were less likely to report ever using condoms (OR=0.2; 95% CI: 0.03-0.8) than women reporting some condom use [Smith 2001]. Similarly, monogamous women in Costa Rica were less likely to report condom use if they were HSV-2 seropositive (seroprevalence of 44.3% among women who reported never using condoms vs 33.5% for women using condoms with a partner for 1-3 months, vs 28.9% for women using condoms for >=24 months) [Oberle 1989].

In summary, these existing published studies support different conclusions regarding the effectiveness of condoms in reducing the risk of HSV-2 transmission and acquisition. However, the evidence provided by each of these studies must be examined in light of the individual study design and populations participating in the study.

3. HSV-1 serological status

Prior HSV-1 infection (HSV-1 seropositivity) may reduce the risk of acquiring HSV-2 infection, although study data are not consistent. In a northern California women's prevalence study, HSV-1 seropositive women had an adjusted odds of 0.7 (95% CI: 0.5-1.0) for HSV-2 prevalence compared to HSV-1 seronegative women [Buchacz 2000]. Two large controlled studies recently conducted to investigate the efficacy of an HSV-2 glycoprotein vaccine showed a trend toward a protective effect of HSV-1 seropositivity in the susceptible partner in reducing HSV-2 acquisition among women but not men [Stanberry 2002]. In contrast, natural history data obtained from two large studies of an ineffective HSV-2 vaccine indicated that HSV-1 serostatus of the susceptible partner did not influence risk of HSV-2 acquisition, regardless of gender [Corey 1999a]. However, Mertz et al found that the highest annual rate of transmission (31.8%) was observed in susceptible female partners who were seronegative for both HSV-1 and HSV-2 at study

entry; a numerically lower transmission rate of 9.1% was observed in susceptible females who were HSV-1 seropositive and HSV-2 seronegative at enrollment [Mertz 1992]. In a study evaluating an experimental HSV-2 glycoprotein vaccine, which enrolled susceptible partners regardless of HSV-1 serostatus, HSV-1 seropositive/HSV-2 seronegative recipients of control injections had a lower incidence of acquisition of genital HSV-2 disease than did the HSV-1/HSV-2 seronegative control subgroup, suggesting that prior HSV-1 infection may confer some degree of protection against HSV-2 disease. This protective effect was more pronounced among females (11.9% acquisition in HSV-1/HSV-2 seronegative females compared to 1.2% in HSV-1 seropositive/HSV-2 seronegative females) than among males (4.2% in HSV-1/HSV-2 seronegative males compared to 1.5% in HSV-1 seropositive/HSV-2 seronegative males).

Other data suggest that HSV-1 seropositivity in the source partner may increase the likelihood of transmission to the susceptible partner [Mertz 1992]. In a longitudinal study of HSV-2 acquisition, HSV-2 seronegative participants whose source partner was HSV-1 and HSV-2 seropositive had over twice the risk of HSV-2 acquisition than HSV-2 seronegative participants whose source partner was HSV-2 seropositive only (HR=2.34; 95% CI: 1.14-4.82) after adjusting for gender, age, and number of sexual acts per week [Wald 2001].

4. Engaging in sexual activity during active genital herpes outbreaks

Transmission of HSV-2 is most efficient when sexual activity takes place in the presence of symptomatic genital lesions [Mertz 1992], most likely because the lesions have higher viral titers [Corey 1994; Kinghorn 1994]. Avoiding sexual contact during active clinical outbreaks has been shown to reduce the risk of transmission from as high as 30% to around 10% annually [Mertz 1992; Bryson 1993; Corey 1993; Mertz 1993].

5. Frequency of sexual activity

In a longitudinal study of HSV-2 acquisition, each additional sex act per week during the month prior to study entry increased the risk of HSV-2 acquisition by 10% after adjusting for sex, age, and partner's serostatus (HR=1.10; 95% CI: 1.01-1.19) [Wald 2001].

6. High number of sexual partners

Although data correlating a high number of sexual partners with increased risk of HSV-2 transmission is limited, there are compelling data linking number of sexual partners with increased HSV-2 seroprevalence. In early studies, a high number of sexual partners was associated with HSV-2 prevalence [Johnson 1989; Breinig 1990; Siegel 1992]. In a recent population-based survey of young women in low income neighborhoods of northern California, women with a lifetime number of 2-5 sex partners had an adjusted odds of HSV-2 seropositivity of 2.2 (95% CI: 1.5-3.3) when compared to women with 0-1 lifetime partners. Women with 6-10 lifetime partners and >11 lifetime partners had adjusted odds of HSV-2 seropositivity of 2.9 (95% CI: 1.8-4.7) and 3.9 (95% CI: 2.3-6.7), respectively [Buchacz 2000]. This trend was evident among many ethnicities; however, the trend was most marked among African American women, in whom

prevalence rose dramatically with increasing number of lifetime sex partners. In a study of heterosexual men and women from a primary care clinic, 4-9 lifetime partners (OR=4.3, 95% CI: 2.1-9.1) and >10 lifetime partners (OR=10.8, 95% CI: 5.2-22.3) was associated with HSV-2 infection among women. For men, >10 lifetime partners was associated with HSV-2 infection when compared to men having 1-3 lifetime partners (OR=17.2, 95% CI: 2.2-132) [Wald 1997b]. On adjusting for age, Wald et al. observed the odds of HSV-2 infection was significantly greater among white women with 4-9 lifetime sexual partners (OR=3.4, 95% CI: 1.2-10.5) and ≥10 lifetime sexual partners (OR=10.2, 95% CI: 3.6-32.3) as compared to white women with one to three lifetime partners. For men, greater than or equal to 10 lifetime sexual partners was also associated with an increased odds of HSV-2 infection (OR=10.4, 95% CI: 1.3-83.4) after adjusting for age.

7. HIV infection

Considerable interaction exists in the transmission dynamics of HSV-2 and HIV infections. Recent studies indicate that HSV is among the most common viral co-infection in HIV-infected persons [Buimovici-Klein 1988], with as many as 80% of homosexual men having evidence of HSV infection [Wald 2002a; Mann 1984; Siegel 1992; Enzensberger 1991].

Genital ulcers caused by HSV have been reported to increase the risk of acquisition and transmission of HIV [Wald 2002a; Dickerson 1996; Cameron 1989; Holmberg 1991; Cowan 1993]. Numerous studies have demonstrated an association between genital ulcers and HIV infection, suggesting that genital ulcerations provide an important portal of entry for HIV [Stamm 1988]. Once co-infected, the immunocompromised individual is more likely to experience frequent and severe recurrent episodes of HSV, the severity and persistence of which will parallel the severity of their immune debilitation [Bagdades 1992; Severson 1999; Posavad 1997; Schacker 1998; Augenbraumn 1995]. As immunosuppression becomes more severe, extensive mucocutaneous ulceration occurs; a sharp rise in the proportion of genital ulcers that are HSV-infected has been reported in patients with CD4 counts <50 cells x 10^6/L [Brugha 1997]. Recent studies have also implicated HSV infection as a cause of up-regulation of HIV replication, further enhancing the severity of both diseases [Posavad 1997].

Co-infection with HSV and HIV increases the rate of transmission of HSV by increasing the frequency of genital HSV-2 reactivation and the prevalence of asymptomatic HSV-2 viral shedding [Posavad 1997]. HIV-infected subjects experience more frequent symptomatic and asymptomatic HSV recurrences [Severson 1999]. HSV viral shedding is 4-5 times more prevalent in subjects co-infected with HIV and HSV [Augenbraumn 1995]. Perirectal reactivation is the most common site of HSV isolation. Thus, reactivations are likely to be associated with unrecognized lesions due to difficulty of self examination of this area [Schacker 1998]. Increased opportunity for HSV transmission is therefore thought to result from both the high prevalence of asymptomatic HSV shedding and undetected asymptomatic outbreaks.

Studies have shown that continuous anti-herpes therapy offers advantages over and above that of episodic treatment of recurrent lesions. A meta-analysis of eight controlled,

randomized studies showed that acyclovir therapy for suppression of recurrent HSV infections offered a substantial survival benefit in HIV-infected subjects [Ioannidis 1998]. A survival advantage was seen in studies in which subjects had a high incidence of clinical herpes infections [Heng 1994; Golden 1992; Griffiths 1992; Mole 1997]. Recent CDC guidelines include recommendations for daily suppressive antiherpetic therapy in individuals infected with HIV [CDC Guidelines MMWR 2002].

APPENDIX 3. HSV-2 INFECTION AND NEONATAL HERPES

Primary herpes infections in pregnancy can result in significant maternal morbidity with one of the most devastating consequences of primary maternal infection being transmission to the neonate [Brown 1987; Brown 1997; Brown 2003; Kulhanjian 1992]. Neonatal herpes can result in death or significant neurodevelopmental impairment in the majority of infected babies [Overall 1994; Kimberlin 2001a and 2001b]. Neonatal herpes prevalence estimates are highly variable and range from 1 in 800 to 1 in 5,000 live births in the US [Handsfield 2000; Marques 2000; Whitley 2002]. These rates reflect between 1,110 and 5,000 cases of neonatal herpes annually in the US [Brown 2003]. Thus transmission of HSV-2 to the neonate at the time of delivery is an important public health issue.

The current American College of Obstetrics and Gynecology (ACOG) recommendations for management of herpes in pregnancy are [ACOG Bulletin 2000]:

- Women with primary HSV during pregnancy should be treated with antiviral therapy.
- Cesarean delivery should be performed on women with first-episode HSV who have active genital lesions at delivery.
- For women at or beyond 36 weeks of gestation with a first episode of HSV occurring during the current pregnancy, antiviral therapy should be considered.
- Cesarean delivery should be performed on women with recurrent HSV infection who have active genital lesions or prodromal symptoms at delivery.
- For management of patients at or beyond 36 weeks gestation who are at risk for recurrent HSV, antiviral therapy may be considered, although such therapy may not reduce the likelihood of cesarean delivery.
- In women with no active lesions or prodromal symptoms during labor, cesarean delivery should not be performed on the basis of a history of recurrent disease.

Significant information has recently become available to clinicians that reinforces the importance of pursuing a diagnostic evaluation for HSV-2 infection in pregnant women. This information includes (1) validation of accurate HSV-2 type specific serologic diagnostic tests [Ashley 2000 and 2001]; (2) positive cost/benefit comparison for serology testing and associated treatment [Scott 1998; Baker 2002; Barnabus 2002]; (3) further evidence supporting the safety and efficacy of management options in pregnant patients [Brown 2003; Watts 2003; Scott 2002; Reiff-Eldridge 2000]; (4) evidence that cesarean section significantly reduces the risk of neonatal transmission [Brown 2003]; (5) data defining the risk of neonatal HSV transmission by maternal HSV serologic status [Whitley 2002; Brown 2003]; and (6) evidence that daily anti-herpetic suppressive therapy in an HSV-2 seropositive partner can reduce transmission to a seronegative susceptible partner in a heterosexual, monogamous relationship (Study HS2AB3009).

With regard to cost effectiveness, a decision analysis model has recently been developed to investigate the cost-effectiveness of providing universal type-specific HSV-2 serologic testing to pregnant women unaware of their HSV-2 serostatus and offering appropriate suppressive antiviral therapy [Baker 2002]. Results from this analysis found that, compared to the current standard of care practices, serologic testing for HSV-2 and suppressive antiviral therapy from week 36 of gestation through delivery resulted in an incremental cost per 100,000 pregnant women of $2.4 million ($24 per woman), 15.4 fewer cases of neonatal herpes and 186 fewer cesarean sections. Thus, serologic testing and antiviral therapy for HSV-2 (versus no testing/antiviral therapy) will cost an additional $24,566 for each additional year of life gained. The benchmark for "cost per quality of additional life year gained" (cost/QALY) analysis is $50,000 – analyses delivering a cost/QALY below $50,000 are considered cost effective. It can therefore be concluded that compared to commonly accepted benchmarks for cost-effectiveness, type-specific serologic testing of pregnant women for HSV-2, followed, when necessary, by suppressive anti-viral therapy is a cost-effective intervention.

With regard to the risk and rate of transmission, in a study to assess the effect of serologic status and cesarean delivery on transmission rates of HSV from mother to infant, Brown et al [Brown 2003] enrolled a total of 58,362 pregnant women during a 17 year time period. From the data collected in this study, the risk/rates of neonatal transmission with regard to HSV-1 and HSV-2 serostatus were established. Rates of neonatal herpes infection computed from these data showed that transmission was highest (1 in 1900 live births) for women with no HSV antibodies (primary first-episode HSV during current pregnancy) and was lowest (1 in 8000) for women who were seropositive for both HSV-1 and HSV-2 (recurrent HSV) (Table 36).

Table 36. Transmission Rates of Neonatal HSV by Maternal HSV Serologic Status Among Women Who Delivered at the University of Washington and Madigan Army Hosptial [1]

Maternal HSV serostatus	No./Total (%) of Infants with Neonatal HSV	Rates per 100,000 Live Births (95% CI)
HSV seronegative	6/11,115 (0.054)	54 (19.8-118)
HSV-1 seropositive only	6/23,480 (0.026)	26 (9.3-56)
All HSV-2 seropositive	3/13,795 (0.022)	22 (4.4.-64)
HSV-2 only	2/5,761 (0.035)	35 (4.2-126)
HSV-1 and HSV-2	1/8,034 (0.012)	12 (0.3-70)

1 Brown 2003

Despite cesarean delivery being a standard obstetric practice for management of pregnant women with herpetic lesions at delivery, Brown *et al* were the first to demonstrate that cesarean delivery does provide significant protection against neonatal herpes transmission [Brown 2003](Table 37).

Table 37. Delivery route and Acquisition of Neonatal Herpes in Women with Herpes Simplex virus isolated from the genital tract, stratified presence of lesion [1]

	Neonatal Infection	No Neonatal Infection	Total
Women with lesions present at delivery			
Cesarean	0	60	60
Vaginal	0	14	14
Women with subclinical viral shedding			
Cesarean	1	24	25
Vaginal	9	94	103
Overall			
Cesarean	1	84	85
Vaginal	9	108	117
Total	10	192	202

1 Brown 2003

When this new information is critically examined, it becomes clear that obstetricians and pediatricians now have available various strategies to identify and possibly reduce acquisition of HSV-2 infection during pregnancy and potentially minimize the risk of herpes transmission to neonates.

As the results from GSK study HS2AB3009 are disseminated to health care professionals and the general public, some individuals may wish to extrapolate these results to the pregnant couple. However, it must be remembered that the study population evaluated in HS2AB3009 did not include pregnant women. Unfortunately, a study to specifically assess the effect of suppressive treatment of the infected male source partner on HSV transmission to a susceptible pregnant partner is not likely to be conducted given the relatively low frequency of acquisition during parturition and the large number of subjects that would be required. Nonetheless, the efficacy of antiviral suppression in the infected male partner (namely, reductions in numbers of episodes as well as days of and quantities of viral shedding) will be the same as that previously documented for Valtrex.

The successful implementation of a health care program that promotes safer sexual practices combined with selective use of Valtrex suppressive therapy to reduce transmission of HSV-2 could ultimately lead to a reduction in the occurrence of HSV-2 acquisition during pregnancy and subsequent decrease in the incidence of neonatal herpes.

APPENDIX 4. HSV RESISTANCE TO ACYCLOVIR

1. Mechanism of drug resistance

The inhibitory activity of acyclovir (the active form of valacyclovir) is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV, VZV and EBV; in the case of CMV, this activity is mediated by a protein kinase encoded by the UL97 gene. TK converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. Acyclovir acts to inhibit HSV replication by inhibiting viral DNA polymerase and terminating growing DNA strands.

In vitro resistance of HSV-1 and HSV-2 to acyclovir results from naturally occurring mutations in the viral genes encoding TK or DNA polymerase [Coen 1980; Elion 1977; Elion 1993]. Such mutations occur in the absence of acyclovir and resistant virus isolates most often lack TK activity (TK-deficient), less often have altered TK substrate specificity (TK-altered) and rarely have a DNA polymerase alteration in substrate specificity. Viruses with TK mutations are normally cross-resistant to other drugs dependent upon the viral TK for activation, such as penciclovir, but generally remain susceptible to DNA polymerase-dependent antiviral agents such as foscarnet and cidofovir. The less common or rare viruses with TK-altered mutations or DNA polymerase mutations may display more complex *in vitro* cross-resistance patterns. Lack of *in vitro* susceptibility of HSV isolates to acyclovir from immunocompromised individuals, as measured by the plaque reduction assay, has been correlated with unsuccessful acyclovir treatment; however, this correlation is not absolute [Safrin 1994]. HSV resistance to acyclovir and related drugs has been reviewed recently in the literature [Bacon 2003; Field 2001].

The first clinical report of an HSV isolate resistant to acyclovir appeared in 1982, early in the history of the drug's use [Crumpacker 1982]. This acyclovir-resistant isolate was obtained from an immunocompromised patient. Since that early report, acyclovir-resistant isolates have also been recovered from immunocompetent patients [Christophers 1998; Field 2001] and several reports have documented acyclovir-resistant strains of HSV from subjects who have never been treated with acyclovir [Barry 1986; McLaren 1993; Lehrman 1986].

2. Antiviral resistance in immunocompetent patients

According to several surveys, the isolation of HSV resistant to acyclovir or other antiherpetic agents is rare in the immunocompetent population (<1%) [Bacon 2003; Christophers 1998; Field 2001]. Data from extensive surveys conducted in the UK and US provide baseline information on the susceptibility of HSV isolates from immunocompetent individuals who have not been exposed to acyclovir (see Table 41) [Collins 1991; Christophers 1998; Hill 1993; Hill 1995]. The prevalence of resistant virus in these surveys was 0.3% and 2.5% (plaque reduction and dye uptake assay, respectively) for untreated subjects. It has been found that the dye uptake assay is likely to overestimate the number of HSV isolates predicted to be resistant as a result of the

amplification of minor subpopulations of resistant variants. In contrast, the plaque reduction assay provides a more accurate reflection of the viral population replicating in the patient at the time of isolation and may therefore give a more reliable prediction of clinical response to antiviral therapy [McLaren 1983]. The plaque reduction assay has largely supplanted the dye reduction assay and has been published as a standard by the National Committee for Clinical Laboratory Standards [Hodinka 2000].

Overall, in the same surveys, the prevalence of resistant virus was similar among isolates from acyclovir-treated subjects (0.5% and 3.2% in plaque reduction and dye uptake assays, respectively) and untreated individuals (0.3% and 2.5%) (see Table 38). Additionally, a collaborative surveillance system for acyclovir-resistant HSV has been established in the US through the CDC and the Task Force on Herpes Simplex Virus Resistance to estimate the prevalence of acyclovir-resistant genital HSV among immunocompetent patients with sexually transmitted diseases (STD) and patients infected with human immunodeficiency virus (HIV) [Reyes 2003; Gnann 1999]. The results of this surveillance between 1996 and 1998 for treated immunocompetent patients (1644 isolates) was comparable to other surveys (acyclovir resistance in 0.18% of isolates). Most recently, a survey for penciclovir resistance reported two resistant isolates out of 1035 isolates (0.19%) obtained from 2 of 585 (0.34%) immunocompetent, treated patients [Sarisky 2002]. Notably, both resistant isolates were transient in that subsequent isolates from these patients were susceptible to penciclovir and acyclovir.

Table 38. Prevalence of acyclovir-resistant HSV in untreated and treated immunocompetent patients

Source		Isolates	Resistant variants	%
Plaque reduction assay [1, 2]				
Untreated				
	Wellcome: UK data (1980-1991)	379	0	0
	Christophers *et al* (1991-1993)	760	3	0.4
	Total	1,139	3	0.3
Treated				
	Wellcome: UK data (1980-1991)	420	2	0.5
	Christophers *et al* (1991-1993)	162	1	0.6
	Total	582	3	0.5
Dye uptake assay [3]				
Untreated				
	Wellcome: US data (before 1980)	304	8	2.6
	Wellcome: US data (after 1980)	1,521	38	2.5
	Total	1,825	46	2.5
Treated				
	Wellcome: US data	976	31	3.2

1. Plaque reduction assay: Collins 1991.
2. Plaque reduction assay: Christophers 1998.
3. Dye uptake assay: Hill 1993, Hill 1995.

3. Antiviral resistance in immunocompromised patients

Isolation of HSV resistant to acyclovir occurs more frequently in immunocompromised compared to immunocompetent individuals [Field 2001; Bacon 2003]. Almost 20 years ago, Wade et al. reported a prevalence rate of acyclovir-resistant HSV ranging from 2% to 9% in bone marrow recipients treated with acyclovir [Wade 1983](Table 37). Similar results were reported by Englund et al. [Englund 1990]. With the increase in the immunocompromised population due to HIV infection and AIDS, reports of resistant isolates have increased while the actual frequency of resistance has not [Erlich 1989; Kimberlin 1996; Bacon 2003]. More recently a CDC surveillance study reported an incidence of acyclovir-resistant HSV strains of 5.3% in this population [Reyes 2003]. Similar results have been obtained in other studies (Table 39) and underscores the fact that the prevalence of resistant HSV in this population is stable. Most recently viral resistance to acyclovir following the use of Valtrex suppressive therapy was evaluated in HIV-infected subjects in study HS230018. In this study, a similar incidence of acyclovir-resistance was observed (three acyclovir-resistant isolates (3/50, 6.0%;) [GSK Report RM2002/00028/00].

Table 39. Prevalence of acyclovir-resistant HSV in immunocompromised patients

Study	Assay method	Reason for immunosuppression	Number of patients shedding HSV	Number of patients with ACV-resistant HSV	%
US					
Wade 1983	Dye uptake	BMT [1.]	74	3	4.2
Englund 1990	Viral DNA inhibition	BMT, HIV, organ transplant, malignancy, high dose steroids, neonate	148	7	4.7
Reyes 2003	Plaque reduction	HIV	226	12	5.3
Gnann 1999 [2, 3]	Plaque reduction	HIV	216	12	5.5
Hill 1995	Dye uptake	BMT	104	9	6.3
UK					
Christophers 1998	Plaque reduction	BMT, heart or lung transplant, HIV, malignancy	95	6	6.3
France					
Nugier 1992	Dye uptake	Transplant, HIV or malignancies	184	17	9.2
Aymard 1995	Dye uptake	Transplant or HIV	750	37	4.9

1. BMT denotes bone marrow transplant.
2. Task Force on HSV Resistance.
3. Data presented represent number of isolates tested and number of isolates classified as ACV-resistant since multiple isolates were obtained from some patients.

It has been found that use of prophylactic antiviral regimens reduces the number of replicating viruses which, in turn, is thought to decrease the likelihood of viral mutations [Ambinder 1984]. It has been proposed that the increased incidence of acyclovir-resistant HSV strains in HIV-infected subjects may be due to increased replication of attenuated strains allowed by decreased immune function [Field 2001; Bacon 2003]. Therefore, it has been hypothesized by some investigators that use of suppressive antiherpetic therapy in HIV-infected subjects may actually decrease the probability of resistance [Severson 1999]; this hypothesis does not yet have experimental confirmation.

4. Transmission of resistant HSV

To date there has been no unequivocal evidence of transmission of an acyclovir-resistant HSV strain from person to person, although this remains a theoretical possibility. A single publication [Kost 1993] reports a case study in which transmission of a resistant HSV strain is described as a possibility; however, paired source and patient isolates required for proof of transmission were not available for analysis. This limited information is despite clinical use of acyclovir for over two decades and the fact that resistant virus exists in the population and, in some instances, can cause clinical disease. The absence of documented transmission of acyclovir-resistant HSV is in stark contrast to other virus and drug combinations such as HIV and antiretrovirals as described by Romano et al. [Romano 2002]. One of the reasons for this paucity of data may be that almost all acyclovir-resistant mutants are TK-deficient (95% on average) and such mutants have reduced pathogenicity and greatly impaired ability to reactivate from latency in animal models [Coen 1994]. Therefore, the great majority of resistant strains are likely to be less biologically competent in the normal human infection and transmission cycle. The apparent decreased ability of acyclovir-resistant mutants to be transmitted may be one of the reasons why the prevalence of resistant HSV has been stable for the 20 years in which acyclovir therapy has been used. While very rare strains of acyclovir resistant HSV which retain pathogenicity have been reported, there is no evidence that they have established additional infections in the population [Hwang 1994; Horsburgh 1998; Swetter 1998], even though one was isolated more than a decade ago [Grey 2003, in press].

5. Alternative treatment for acyclovir-resistant infections

Acyclovir-resistant HSV infections have been treated successfully with foscarnet [Safrin 1991; Safrin 1994; Chatis 1989; Jones 1995] and with cidofovir [Lalezari 1994; Lalezari 1997; Snoeck 1994]. These agents act directly at the level of DNA polymerase and do not require phosphorylation by TK; both are effective *in vitro* against both TK-deficient and TK-altered HSV mutants [Gaudreau 1998]. However, a few DNA polymerase mutants resistant to acyclovir are also cross-resistant to foscarnet and cidofovir.

6. Antiviral resistance modeling

Blower and colleagues have developed an antiviral epidemic mathematics model of HSV-2 to predict levels of antiviral drug resistance that would emerge if treatment rates for genital herpes were substantially increased [Blower 1998]. The model represents the

linked transmission dynamics of drug-sensitive and drug-resistant HSV-2 in an immunocompetent community where patients receive either episodic therapy or no therapy. HSV-2 resistance could emerge within three scenarios: (1) susceptible individuals could acquire drug-resistant infection through sexual contact with an individual who has drug-resistant HSV-2, (2) HSV-2 resistance could develop due to acquired permanent resistance, or (3) HSV-2 resistance could occur due to acquired transient resistance. Predictions were based upon the assumptions that drug-resistant and drug-sensitive viruses differed only in their transmissibility and that drug-sensitive strains are more infectious than drug-resistant strains [Blower 1998, Gershengorn 2000].

Assuming that antiviral usage is high (i.e., that 10-50% of the individuals who were shedding virus at any particular time could receive episodic treatment), only low levels of drug resistance are predicted to emerge even over a period of decades. Under the assumption that drug-resistant strains will only be attenuated in their ability to infect, it was predicted that only 7 in 1,000 individuals at 25 years are expected to be shedding drug-resistant strains and that even after 25 years of high antiviral usage, 4.5 cases of HSV-2 would be prevented for each prevalent case of drug-resistant HSV-2 [Blower 1998; Gershengorn 2000]. Assuming that drug-resistant strains will be less infectious and less likely to reactivate, only 5 out of 10,000 individuals are predicted to be shedding drug-resistant virus; furthermore, after 25 years, 52 cases of HSV-2 would be prevented for each prevalent case of drug-resistant HSV-2 [Gershengorn, in press]. Thus, increasing episodic treatment rates (in an immunocompetent population) would mildly, yet significantly, decrease the incidence of HSV-2 infections. The actual impact of increased treatment rates on the incidence of new infections has not been determined, and in the model of White and Garnett [White 1999], decreased incidence was not demonstrated. Importantly, and in contrast to the analogous situation with HIV and antiretroviral drugs, the prevalence of drug-resistant HSV-2 strains would remain low, even after several decades [Blower 1998; Gershengorn 2000; Gershengorn, in press]. A very similar conclusion was reached in modeling of increased rates of topical treatment of herpes labialis, in which significant increases in resistance prevalence were not predicted for decades following the treatment increase [Lipsitch 2000].

7. Conclusions

In summary, the prevalence of acyclovir-resistant HSV has remained low and stable despite increasing clinical use of antiviral agents directed at herpes viruses for over two decades. A unique combination of virus-, host- and drug-related factors explains why resistance has not emerged in the general population and also why potentially increased suppressive use of Valtrex as a result of the added benefit of reduced transmission is unlikely to increase the prevalence of acyclovir-resistant HSV.

APPENDIX 5. SAFETY AND EFFICACY OF VALTREX AS SUPPRESSIVE THERAPY FOR RECURRENT GENITAL HERPES

The safety and efficacy of valacyclovir for the suppression of genital herpes infections in immunocompetent subjects have been described previously [GSK Document BQRT/96/0001; Reitano 1998]. Study data are summarized below.

1. Efficacy of suppressive Valtrex treatment

The efficacy of Valtrex for suppression of genital herpes was previously evaluated in a randomized, double-blind, placebo-controlled study (Study 026) which enrolled 1479 immunocompetent adults with a history of 6 or more recurrences per year. Six treatment regimens (4 Valtrex arms, 1 Zovirax arm, 1 placebo arm) were investigated for 52 weeks in this study: Valtrex 1000mg once daily, Valtrex 500mg once daily, Valtrex 250mg once daily, Valtrex 250mg twice daily, Zovirax 400mg twice daily, and placebo.

Study results provided evidence that Valtrex successfully suppresses recurrent genital herpes. Proportions analyses showed a significant increase in the proportion of patients who were recurrence-free at 6 months [GSK correspondence to FDA, 24 February 1997] and 12 months in the Valtrex groups relative to placebo [GSK document BQRT/96/0001]. Proportions results for the overall population are presented in Table 40 for Valtrex 500 mg qd, Valtrex 1000 mg qd and placebo; data are also stratified according to number of genital herpes recurrences per year (>9 or ≤9) since a previous study had shown a relationship between recurrence history and the recurrence rate and time to recurrence [Patel 1996].

Table 40. Proportions of Patients Recurrence-Free at 6 and 12 Months (overall population and stratified by >9 and ≤ 9 recurrences per year)

	Percentage of Patients Recurrence-Free					
	6 months (≤ 9 recur.)	12 months (≤ 9 recur.)	6 months (>9 recur.)	12 months (>9 recur.)	6 months (overall)	12 months (overall)
1000 mg qd	57%	36%	53%	32%	55%	34%
500 mg qd	52%	31%	36%	23%	47%	28%
Placebo	7%	3%	6%	6.2%	7%	4%

At 12 months, 34% of patients receiving Valtrex 1000mg qd and 28% of those receiving Valtrex 500 mg were recurrence-free compared to 4% in the placebo group (relative risk 0.65 [95% CI; 0.572, 0.739] for 1000 mg qd; relative risk 0.69 [95% CI; 0.604, 0.787] for 500 mg qd). Kaplan-Meier analysis demonstrated that all doses of Valtrex were effective in delaying or preventing recurrent genital herpes infections during the study periods compared to placebo. Valtrex 1000mg delayed or prevented 78% of the recurrences experienced by placebo patients during the 12 month study period (hazard ratio 0.22 [95% CI: 0.17, 0.29], $p < 0.001$). Valtrex 500mg once daily delayed or prevented

approximately 71% of the recurrences experienced by placebo patients during the 12-month study period [hazard ratio 0.29 (95% CI: 0.22, 0.37), p < 0.001].

Of note, subjects with 9 or fewer recurrences per year showed comparable results with Valtrex 500mg once daily compared to Valtrex 1000mg qd. For this reason, a 500mg once daily suppressive dose was recommended as an appropriate dose for this population in the product label and was selected for use in Study HS2AB3009 (in which eligible source partners were required to have a history of ≤9 genital herpes recurrences per year).

2. Safety of suppressive Valtrex treatment

In Study 123-026, there was no evidence of an increased incidence of AEs in Valtrex recipients in any dose group compared with acyclovir or placebo recipients. Of the 1479 subjects enrolled, 1245 patients (84%) reported one or more AEs. For completeness, AE data for the four Valtrex treatment arms (1000mg once daily, 500 mg once daily, 250mg once daily, and 250mg twice daily) were pooled for comparison to acyclovir and placebo. The most common events occurring in ≥5% of subjects in any treatment group were headache, rhinitis and infection. As shown in Table 41, the distribution of AEs within each treatment group did not differ appreciably among Valtrex, acyclovir and placebo.

Table 41. Summary of Frequent Adverse Events Reported by ≥5% of Immunocompentent subjects in Genital Herpes Suppression Study 123-026

Adverse Event	Placebo N=134 n (%)	Valtrex N=1078 n (%)	Acyclovir N=267 n (%)
Headache	45 (34)	383 (36)	100 (37)
Rhinitis	24 (18)	244 (23)	66 (25)
Infection	22 (16)	180 (17)	56 (21)
Flu Syndrome	17 (13)	180 (17)	49 (18)
Pharyngitis	19 (14)	115 (11)	29 (11)
Nausea	11 (8)	115 (11)	33 (12)
Back pain	8 (6)	100 (9)	34 (13)
Diarrhea	19 (14)	97 (9)	32 (12)
Abdominal pain	6 (4)	95 (9)	20 (7)
Pain	7 (5)	93 (9)	21 (8)
Sinusitis	4 (3)	86 (8)	31 (12)
Injury Accident	5 (4)	78 (7)	27 (10)
Dysmenorrhea	11 (8)	67 (6)	21 (8)
Dyspepsia	10 (7)	66 (6)	18 (7)
Rash	5 (4)	65 (6)	15 (6)
Arthralgia	7 (5)	61 (6)	20 (7)
Depression	6 (4)	58 (5)	10 (4)
Allergic Reaction	3 (2)	58 (5)	11 (4)
Urinary Tract Infection	3 (2)	52 (5)	18 (7)
Bronchitis	3 (2)	52 (5)	14 (5)
Myalgia	3 (2)	50 (5)	21 (8)
Asthenia	7 (5)	48 (4)	8 (3)
Reaction unevaluable	3 (2)	42 (4)	13 (5)
Migraine	3 (2)	40 (4)	13 (5)

Blood chemistry and hematology monitoring revealed no clinically important differences over time or among treatment groups.

Sixty serious adverse events were reported in 48 subjects in Study 123-026; 4 events were considered possibly related to study medication (Table 42). One subject randomized to Valtrex 250mg twice daily experienced leukopenia, which was considered as life-threatening by the investigator, and the subject permanently discontinued the study. Another subject randomized to Valtrex 1000mg once daily experienced hepatitis and permanently discontinued study drug.

Two subjects who received acyclovir 400mg twice daily experienced serious adverse events considered related to study medication by the investigator. One subject had myasthenia in his left arm and leg; the second experienced depression and was hosptialized overnight. Lastly, one patient in the Valtrex 250mg once daily group died of bronchial asthma. The investigator did not consider the death attributable to study medication.

Table 42. Summary of Serious Adverse Experiences Reported by Immunocompetent Subjects in Genital Herpes Suppression Study 123-026 [1]

Serious Adverse Event	Placebo N=134 n (%) [2]	Valtrex N=1078 n (%)	Acyclovir N=267 n (%)
Reaction unevaluable [3]	0	6 (1)	1 (0)
Depression	1 (1)	4 (1)	1 (0) [4]
Injury/ Accident	1 (1)	2 (0)	0
Abortion	0	2 (0)	1 (0)
Hepatitis	0	2 (0) [4]	0
Pyelonephritis	0	2 (0)	0
Bone disorder	0	1 (0)	0
Bronchitis	0	1 (0)	0
Bronchospasm	0	1(0)	0
Cyst	0	1 (0)	0
Pulmonary Embolism	0	1 (0)	0
Gastritis	0	1 (0)	0
Headache	0	1 (0)	0
Heart Failure	0	1 (0)	0
Hematuria	0	1 (0)	0
Leukopenia	0	1(0) [4]	0
Meningitis	0	1(0)	0
Metrorrhagia	0	1 (0)	0
Migraine	0	1 (0)	0
Neoplasm skin	0	1 (0)	0
Peripheral neuritis	0	1 (0)	0
Intestinal Obstruction	0	1 (0)	0
Pain	0	1 (0)	0
Abdominal pain	0	1 (0)	0
Suicide attempt	0	1 (0)	0
Uterine fibroid enlargement	0	1 (0)	0
Vascular disorder	0	1 (0)	0
Colitis	0	0	1 (0)
Convulsion	0	0	1 (0)
Dehydration	0	0	1 (0)
Endometrial Disorder	0	0	1 (0)
Urinary Tract Infection	0	0	1 (0)
Myasthenia [3]	0	0	1 (0)
Breast neoplasm	0	0	1 (0)
Salpingitis	0	0	1 (0)
Vestibular disorder	0	0	1 (0)

[1] Except when noted, SAEs were considered not attributable to study drug

[2] Number and percent of patients experiencing the event

[3] 'Reaction unevaluable' was the coded term assigned to the following recorded SAEs (none of which were considered attributable to study drug): ruptured appendix, appendectomy, ureterovaginal fistulation, acute appendicitis (reported in two subjects), food poisoning, and retained products of conception.

[4] SAE considered possibly or reasonably attributable in 1 subject

3. Conclusions: suppressive Valtrex therapy

The conclusions from this study of Valtrex for the suppression of genital herpes in immunocompetent subjects were that:

- Valtrex 500mg and 1000mg once daily significantly delayed or prevented the recurrence of genital HSV for a period of up to one year compared with placebo.
- The recommended dosage of Valtrex for chronic suppressive therapy in patients with >9 recurrences per year is 1000mg once daily. In patients with ≤9 recurrences per year, Valtrex 500 mg once daily is an appropriate dose.
- All doses of Valtrex studied were well tolerated for up to 12 months of suppressive treatment.

APPENDIX 6. LONG-TERM SAFETY EXPERIENCE WITH ACYCLOVIR AND VALACYCLOVIR

Seven years after FDA approval of Valtrex and two decades after the introduction of Zovirax, a wealth of data has been generated on the clinical safety and efficacy of this selective antiherpes agent and its prodrug. The clinical development program for Valtrex has involved over 10,000 patients in clinical trials up to one year in duration. In addition, more than 20 million prescriptions for Valtrex have been dispensed in the US.

Experience with acyclovir – long term use in genital herpes

In 1984, approximately 1100 immunocompetent adults with frequently recurring genital herpes were enrolled in a 10 year study of oral acyclovir for suppression of outbreaks (Study P12-123) [Mertz 1988; Baker 1995]. This multicenter study was double-blind during the first year, when patients were randomized to receive suppressive acyclovir 400 mg twice daily or placebo (recurrences were treated with open-label acyclovir 200 mg 5 times daily for 5 days). An open-label design was adopted in the second year, when patients could elect to receive either episodic or suppressive therapy. During years 3-6, patients could choose open-label continuous suppressive acyclovir therapy. During year 7, patients were given only episodic therapy with acyclovir 200 mg 5 times daily for 5 days; those who had two or more genital herpes recurrences during this year were subsequently offered suppressive therapy with acyclovir 400 mg twice daily during years 8-10.

1. Subject Accountability

In Study P12-123, 950 patients completed the first year of the study. Seven hundred eighty three (783) patients entered and 683 completed year two. After five years of therapy, 389 patients remained in the study and 265 patients completed seven years.

Most of the patients who discontinued from the study did so during the two year placebo-controlled portion of the study. Over twice as many placebo as drug-treated patients were lost to follow-up (most common reason for discontinuation) or desired to leave the trial during the first two years. The second most common reason for leaving the study was site discontinuations. There were 7 deaths: one accidental, one pancreatic cancer and five AIDS-related deaths. Twenty patients discontinued because of an AE; seven of these were laboratory abnormalities. Three of these abnormalities could have been related to alcohol abuse. For the remaining four, laboratory measures normalized shortly after discontinuing the study. Thirteen patients discontinued due to clinical AEs such as diarrhea, gastrointestinal distress, headache, alopecia, hirsutism, skin changes, allergic reaction, melanoma (1 patient) and two central nervous system events (dizziness and imbalance).

2. Safety Results

During the double-blind phase of the study, AEs events were similar in frequency for patients randomized to acyclovir or placebo. The most frequent AEs were nausea,

diarrhea, and headache. Throughout the 10 year study, AEs were infrequent, mild and generally considered unrelated to treatment. There was no evidence of drug-related SAEs or cumulative toxicity (Table 43). Acyclovir was reported to be well tolerated during the 10 year study [Tyring 2002].

Table 43. Frequencies of most common AEs (%) among patients receiving continuous acyclovir suppressive therapy for ≤10 years [1]

Yr	Therapy (n)	Nausea	Diarrhea	Head-ache	Rash	Asthenia	Dizziness	Abd. Pain	Vaginitis
1	S[2] (586)	4.8	2.4	1.9	1.7	1.2	1.2	0.9	1.1
	E[2] (589)	2.4	2.7	2.2	1.5	1.2	1.2	1.7	0
2	S (698)	0.7	0.1	1.9	1.1	0.2	1.1	1.1	0.3
	E (85)	1.1	1.1	2.4	0	0	2.4	0	2.3
5	S (430)	0.2	0.2	1.2	0	0.2	0	0.2	1.7
9	S (152)	0	0.7	1.3	0	0	0	0.7	0

[1] Mertz 1988b

[2] E = episodic therapy (200 mg 5 times/day for 5 days); S = suppressive therapy (400 mg bid)

3. Acyclovir Resistance

Of the approximately 1100 immunocompetent patients enrolled in this long-term acyclovir suppression study, a cohort of 239 patients (who discontinued suppressive therapy during the seventh year of the study) was followed for development of acyclovir resistance after receiving ≥ 6 years of chronic suppressive therapy [Fife 1994]. During the one year follow up period, 85.8% of these patients had at least one recurrence and 75% had at least two recurrences. Viral isolates were measured for acyclovir sensitivity using the dye uptake assay method. Median acyclovir sensitivity for 113 viral isolates was 0.79 µg/mL (65.5% were highly sensitive). Four isolates (3.5%) were considered to be resistant (acyclovir sensitivity ≥3 µg/mL). These values are comparable to values from pre-therapy isolates and also to values reported from patients who had never taken acyclovir. Resistance post-therapy was similar to that reported pre-therapy (3.7% resistant isolates in 107 specimens). Of note, one patient whose viral isolate was resistant to acyclovir prior to initiating therapy had only acyclovir-sensitive virus isolated after discontinuation of prolonged suppression therapy, suggesting transient resistance. Thus, even after 6 years of acyclovir suppressive treatment, most patients continued to have recurrences upon cessation of chronic suppressive therapy, yet selection of resistant virus was not observed [Fife 1994].

Experience with Valtrex – long term safety in genital herpes

Three randomized controlled trials and one open-label study demonstrated the efficacy and long term safety of oral Valtrex for suppression of recurrent genital herpes infection (Table 44) [Reitano 1998; Patel 1997a; Conant 2002; Baker 1999]

Table 44. Patients treated in efficacy trials of Valtrex for suppression of recurrent HSV infection

Study (Reference)	Subject Population	Total Subjects	No. of Valtrex recipients	Total daily Valtrex dose (mg)	Treatment comparison	Trial duration
1 (Patel 1997) [1]	Immuno-competent	382	288	500	Placebo	16 weeks [2]
2 (Reitano 1998) [3]	Immuno-competent	1479	269 540 269	250 500 1000	Acyclovir (800mg) Placebo	1 year
3 (Baker 1999)	Immuno-competent	127	127	500	----------	1 year
4 (Conant 2002) [4]	HIV-infected	1062	713	1000	Acyclovir (800mg)	1 year
Total		3050	2206			

[1] Study 34,526-037, submitted to NDA 20-550 as S-003 on November 18, 1996.
[2] In all, 313 patients continued with open-label Valtrex to complete 1 year of therapy.
[3] Study 34,526-026, submitted to NDA 20-550 as S-003 on November 18, 1996.
[4] Studies 34,526-007 and 34,526-008, submitted to NDA 20-550 as S-005 on April 23, 1997.

1. Adverse events

In these studies, which supported the approval of Valtrex suppressive therapy for genital herpes infections, subjects receiving Valtrex, acyclovir, or placebo reported AEs similar in nature and incidence (see Table 45) [Tyring 2002]. There was no apparent relationship between the total daily exposure to Valtrex and the nature, severity, or frequency of the most common AEs. The most frequent AEs among immunocompetent patients receiving Valtrex or acyclovir were headache, infectious illness (e.g., influenza, common cold, rhinitis, sinusitis) and nausea. Long term therapy with Valtrex was not associated with hematologic or clinical chemistry laboratory abnormalities, with no meaningful differences among Valtrex, acyclovir, and placebo treatment groups [Tyring 2002].

Table 45. Most common AEs (%) in subjects receiving Valtrex (250-1000mg/day) or acyclovir (800 mg/day) for up to 1 year

SUBJECT TYPE					
	Immunocompetent [2,3,4]		HIV-Infected [5]		
Event	Valacyclovir n = 1493 (%)	Acyclovir n = 267 (%)	Placebo n = 228 (%)	Valacyclovir n = 713 (%)	Acyclovir n = 349 (%)
Headache	32 (12) [1]	37 (12)	25 (3)	18 (5)	17 (7)
Rhinitis	20 (<1)	25 (<1)	15 (0)	12 (<1)	12 (0)
Infection	15 (2)	21 (0)	11 (0)	18 (0)	13 (1)
Nausea	10 (6)	12 (6)	8 (7)	12 (6)	14 (5)
Pharyngitis	9 (1)	11 (0)	10 (<1)	11 (0)	13 (0)
Diarrhea	8 (3)	12 (5)	10 (4)	20 (5)	19 (4)
Abdominal pain	8 (3)	7 (3)	4 (3)	11 (3)	7 (2)
Rash	6 (1)	6 (1)	7 (1)	15 (1)	14 (2)
Depression	4 (1)	4 (1)	3 (1)	10 (1)	11 (0)
Fever	2 (<1)	<1 (0)	1 (0)	10 (0)	11 (<1)
Any Event	82 (32)	85 (31)	67 (24)	77 (28)	77 (25)

1 Parentheses denote percentage of patients wth an event attributed to drug

2 Reitano 1998

3 Patel 1997a

4 Baker 1999

5 Conant 2002

AEs such as rash, fever, diarrhea and depression in HIV-infected subjects could all be related to concomitant diseases, HIV infection, concurrent medications, or the increased sensitivity of the HIV-infected subjects to drug associated rash.

2. Serious Adverse Events

Within these four studies, SAEs occurred in 2.4% of immunocompetent subjects and were thought to be possibly attributable to study medication for 0.2% of Valtrex recipients (leukopenia, hepatitis and headache) and for 0.7% of acyclovir recipients (myasthenia and suicidal ideation). The death of one subject from bronchial asthma was not attributed to Valtrex therapy. In HIV-infected subjects, SAEs were reported in 10.5% of the population, with attribution to study treatment in 1.1% of Valtrex recipients and 0.9% of acyclovir recipients. These events were most commonly associated with gastrointestinal disturbances and headache.

3. Deaths

There were 8 deaths in Valtrex recipients (2 subjects each: AIDS progression, homicide, sepsis/septic shock; 1 subject each: suicide, pneumonia). None of these deaths were considered possibly related to study drug.

Conclusions

The large number of patients studied in clinical trials over an extended period of time in combination with many years of postmarketing experience has afforded considerable confidence in the safety of long-term suppressive therapy with valacyclovir at doses up to

1000mg/day. Comparable safety profiles were observed for Valtrex, acyclovir and placebo in randomized controlled trials. Of note, data from over 900 subjects enrolled in the open-label phase of HS2AB3009 will be available after June 2003, including 20 month safety data for a subset of patients enrolled in this study.

APPENDIX 7. REVIEW OF THROMBOTIC MICROANGIOPATHIES IN IMMUNOCOMPROMISED PATIENTS TREATED WITH VALTREX

Thrombotic Thrombocytopenic Purpura (TTP) and/or Hemolytic Uremic Syndrome (HUS) are disease entities within the broader Thrombotic Microangiopathy (TMA) categorization. TTP/HUS have been observed in immunocompromised and HIV-infected patient populations treated with Valtrex.

Diagnosis of TTP is based on microangiopathic hemolytic anemia, thrombocytopenia, renal abnormalties and/or neurological abnormalities and fever. HUS covers a similar spectrum of signs and symptoms, including microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The incidence of TTP or HUS has been estimated to be 1:90,000 in a general population [US National Center for Health Statistics 1990]. However, several severe illnesses, principally those that include significant depression of normal immune function, are associated with a higher risk, e.g., sepsis, CMV infection, mycobacterium avium complex, malignancies (particularly those affecting lymphocyte function), and HIV (particularly those with low CD4+ cell counts) [Feinberg 1998; Lowance 1999]. A number of drugs used to treat these conditions are also associated with TTP/HUS, particularly when used specifically to suppress immune function, such as in bone marrow transplant (BMT). Thus, it is difficult to assess the added risk of a drug association when administered in these circumstances.

Due to the severity of TTP/HUS, ongoing surveillance activities are directed toward better understanding the possible relationships between Valtrex use, TTP/HUS, and host factors. A review of clinical trial and postmarketing reports held by GSK is presented below.

1. Valacyclovir for the Prophylaxis of CMV

Early controlled clinical studies with Valtrex administered in high doses (8g/day) for CMV prophylaxis in subjects with HIV, and those undergoing BMT, renal transplant or heart/lung transplant, identified a number of subjects who developed TTP/HUS. These cases are presented in Table 46 below.

Table 46. Summary of TTP/HUS in Valtrex Clinical Studies of CMV Prophylaxis

Study	Population	No. Subjects Received Valtrex	No. Valtrex Subjects With TTP/HUS (%)
123-014	HIV	523	14 (2.7)
123-012	Renal Transplant	306	1 (0.3)
123-016	BMT	311	10 (3.2)
123-039	BMT	71	3 (4.2)
123-031	Heart/Lung Transplant	14	0 (0)
Total in CMV studies		**1225**	**28 (2.3%)**

There has been one further report of TTP/HUS in a GSK clinical study of Valtrex for the prophylaxis of CMV infection in a renal transplant subject.. This subject received a reduced Valtrex dose of 1500mg once daily due to renal impairment. The investigator did not ascribe Valtrex as suspect medication.

The incidence of TTP/HUS observed was highest in BMT and HIV-infected subjects receiving 8g Valtrex/day (3.2% and 4.2% in two studies in BMT recipients, and 2.7% in one HIV study). It should be noted that all HIV subjects who developed TTP/HUS had CD4+ cell counts <50 cells/µL at the time of the event. In consideration of the serious nature of TTP/HUS, these findings led to the inclusion of the WARNINGS statement in the Valtrex Product Information.

However, as to be expected, there were many confounding factors which made it difficult to ascribe the contribution of Valtrex to enhanced relative risk. Subsequent epidemiological studies in the HIV population in ambulatory care and sponsored by GSK have been undertaken. Two outpatient database searches, one study in Australia including 3500 patients, and one study in the US including 4261 patients, revealed incidences of 0.6% and 0.7%, respectively [GSK Document RM1999/00357/00; Gold 1998]. In contrast, a survey of 350 consecutive hospital admissions of patients with HIV revealed an incidence of 7% [Moore 1999]. None of the patients with TTP/HUS in these surveys was taking Valtrex at the time.

2. Valacyclovir For the Treatment or Suppression of Recurrent Genital Herpes in HIV-Infected Subjects

There has been one GSK-sponsored controlled clinical study of the use of Valtrex in the treatment of episodes of recurrent genital herpes in HIV-infected subjects (123-008), and two studies in long-term suppression of recurrent genital herpes in HIV-infected subjects (123-007 and HS230018). A summary of TTP/HUS cases is provided in Table 47 below.

Table 47. Summary of TTP/HUS in Studies of Treatment or Suppression of Genital Herpes

Study	Population	Treatment Protocol	Valtrex Dose(s)/ Duration	No. Subjects Received Valtrex	No. Valtrex Subjects With TTP/HUS (%)
123-008	HIV	Episodic	1000 mg BID/ 5-10 days	230	1 (0.4)
123-007	HIV	Suppression	500 mg BID or 1000 mg QD/ 48 weeks	713	0(0)
HS230018	HIV	Suppression	500 mg BID/ 6 months	194	0 (0)
Total				**1137**	**1 (<0.09%)**

One subject (in Study 123-008) developed HUS. He had been enrolled and allocated Valtrex, to take at the first sign of an episode of recurrent genital herpes. However, he

never returned to the clinic and it was reported 9 months later that he had died of meningeal lymphoma and HUS. It was not known if he had taken Valtrex in relation to these events.

3. Spontaneous Reports of TTP/HUS in Patients Taking Valtrex

A search of the GlaxoSmithKline worldwide safety database was conducted to identify possible cases of TTP and/or HUS that occurred in patients who had been treated with Valtrex as either suspect or concurrent medication. Reports of anemia, schistocytosis, thrombocytopenia, purpura, hematuria, renal insufficiency, renal failure, fever and similar events associated with TTP/HUS were then reviewed against the TTP/HUS decision tree developed by GSK and FDA for use during clinical studies. Any case described as TMA, TTP, or HUS was also included, even if the full set of criteria were not met.

Between the launch of Valtrex in 1995 and 31 March 2002, four postmarketing reports of TTP/HUS in subjects who received Valtrex met the criteria for TTP/HUS as described above; all were in HIV-infected subjects. Of the HIV-infected patients, two were from the US (one in 1996 and one in 2000). A fifth case of TTP/HUS has been subsequently reported, involving a patient with lymphoma and metastatic cancer of the kidneys. The daily dose of Valtrex ranged from 1 to 3 grams, and in one case the daily dose was unknown. The time to onset of TTP/HUS was 3 days in two subjects, 7 days in one subject, 8 weeks in another subject, and 1 year in the last subject. Three cases resolved and two had a fatal outcome. A summary of these cases is given in Table 48 below.

Table 48. Valtrex Post-marketing Reports of TTP/HUS Since Time of Launch (1995)

Case ID Demography Report Source Onset	Dose and Duration of Valtrex therapy	Indication	Time to onset	Medical conditions	Outcome	Concomitant Medications
A0047732A 43 yo M Spontaneous 10/96	1 g tid x 7 days	Herpes zoster	8 weeks	HIV	Fatal (after 3 days)	Lamivudine Stavudine
B0071218A 42 yo M Spontaneous 8/99	2 g x 1d, 3 g x 1d, 1 g x 1d.	Herpes zoster of chest	3 days	HIV	Resolved	Indinavir Lamivudine Stavudine
B0057333A [a] 48 yo M Spontaneous report in 1998; Literature in 2000 5/98	1 g daily x 1 yr	Recurrent ocular herpes simplex	1 year	HIV x 12 years History of toxoplasmosis	Resolved	Stavudine Didanosine Ritonavir Lamivudine Saquinavir Clindamycin Pyrimethamine
A0118657A 34 yo F Spontaneous 3/00	Caplets (UNK) x 3 days	Genital herpes	3 days	HIV	Resolved	Antiretrovirals Co-trimoxazole
A0366756A[a] 40s yo M Spontaneous Unknown	3 g daily (2 week course prescribed)	Ulcerating HSV II	7 days	Lymphoma Metastatic cancer of kidneys	Fatal (a few days after onset)	Unknown

[a] Received after the 31 March 2002 data cut-off date

To put these numbers into perspective, prescription data indicate that over 19 million Valtrex prescriptions have been dispensed in the US since launch in 1995. Furthermore, approximately 21,000 patients in the US who received a prescription for an HIV drug in the period July 2000 through June 2002 also received a prescription for Valtrex [GSK data on file], so GlaxoSmithKline is aware of some base of actual use of Valtrex among patients with HIV infection in the US.

4. Spontaneous Reports of TTP/HUS in Patients Taking Acyclovir

At the request of FDA, the worldwide GSK safety database was also searched for postmarketing reports of TTP/HUS among patients who received acyclovir. Since launch of Zovirax in 1982 and 31 March 2002, 10 postmarketing reports of TTP/HUS were identified. Three cases were in post-transplant/malignancy patients, four occurred in

elderly patients with herpes zoster (including one patient with ophthalmic zoster), two cases were in HIV-infected patients, and in one case the condition was unknown. For nine of the ten cases, the dose of acyclovir was unknown.

5. TTP/HUS in Other Clinical Trial Experience with Valtrex

In controlled clinical studies of Valtrex in the treatment or suppression of recurrent genital herpes involving over 10,000 immunocompetent subjects using doses less than or equal to 2g/day, there have been no reports of TTP/HUS. In addition, there have been no reports of TTP/HUS among approximately 2500 immunocompetent subjects in GSK-sponsored controlled clinical studies using Valtrex doses less than or equal to 4g/day.

APPENDIX 8. POST-MARKETING EXPERIENCE: SPONTANEOUS REPORTS OF SERIOUS ADVERSE EXPERIENCES AND DEATH

From first worldwide marketing of Valtrex in 1995 through end of September 2002, over 19 million Valtrex prescriptions have been dispensed in the US and over 23 million in the leading 7 countries (based on sales data). GlaxoSmithKline's intracompany safety database containing worldwide adverse event reports allows continuous surveillance for spontaneous reports of Valtrex as suspect medication. Spontaneous reports include information from sources such as consumers, health care professionals, regulatory authorities, and the literature.

Due to the nature of these spontaneous reports, case report information is often incomplete. Attempts at follow-up and medical confirmation are pursued but may be unsuccessful or not possible. Also determination of event incidence and frequency from spontaneous data is not possible, nor is a reliable assessment of a causal relationship between an AE and the drug. From the time of marketing of Valtrex in 1995 through 31 March 2002, there have been 29 spontaneous reports with a fatal outcome and 541 serious adverse event reports.

The section of the product label describing adverse events observed during clinical practice is updated when new signals are identified. The events listed represent those chosen for inclusion due to their seriousness, frequency of reporting, causal connection to Valtrex, or a combination of these factors. The following is the current 'Observed During Clinical Practice' section of the Valtrex product label:

Observed During Clinical Practice:

General: Facial edema, hypertension, tachycardia

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritis, rash, and urticaria

Central Nervous System Symptoms: Aggressive behavior; agitation; ataxia; coma; confusion; decreased consciousness; dysarthria; encephalopathy; mania; and psychosis, including auditory and visual hallucinations; seizure

Eye: Visual abnormalities

Gastrointestinal: Diarrhea

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis

Renal: Elevated creatinine, renal failure

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis

Skin: Erythema multiforme, rashes including photosensitivity

APPENDIX 9. PRESCRIBING INFORMATION FOR VALTREX IN THE US

VALTREX®

(valacyclovir hydrochloride)

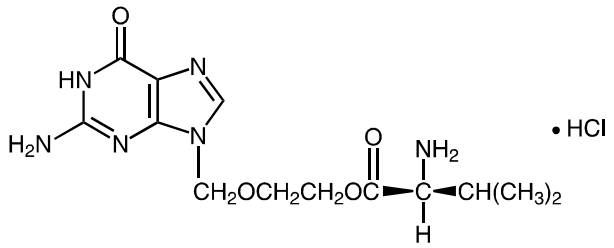
Caplets

DESCRIPTION

VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of *L*-valyl ester of the antiviral drug acyclovir (ZOVIRAX® Brand, GlaxoSmithKline).

VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

The chemical name of valacyclovir hydrochloride is *L*-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester, monohydrochloride. It has the following structural formula:



Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4$•HCl and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/mL. The pk_a's for valacyclovir hydrochloride are 1.90, 7.47, and 9.43.

MICROBIOLOGY

Mechanism of Antiviral Action: Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both in vitro and in vivo.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: 1) competitive inhibition of viral DNA

polymerase, 2) incorporation and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the in vitro susceptibility of herpesviruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

Drug Resistance: Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV and VZV to acyclovir occurs by the same mechanisms. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to valacyclovir (and therefore, to acyclovir) should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY

After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism.

Pharmacokinetics: The pharmacokinetics of valacyclovir and acyclovir after oral administration of VALTREX have been investigated in 14 volunteer studies involving 283 adults.

Absorption and Bioavailability: The absolute bioavailability of acyclovir after administration of VALTREX is 54.5% ± 9.1% as determined following a 1-gram oral dose of VALTREX and a 350-mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the administration of VALTREX is not altered by administration with food (30 minutes after an 873 Kcal breakfast, which included 51 grams of fat).

There was a lack of dose proportionality in acyclovir maximum concentration (C_{max}) and area under the acyclovir concentration-time curve (AUC) after single-dose administration of 100 mg, 250 mg, 500 mg, 750 mg, and 1 gram of VALTREX to 8 healthy volunteers.

The mean C_{max} (± SD) was 0.83 (± 0.14), 2.15 (± 0.50), 3.28 (± 0.83), 4.17 (± 1.14), and 5.65 (± 2.37) mcg/mL, respectively; and the mean AUC (± SD) was 2.28 (± 0.40), 5.76 (± 0.60), 11.59 (± 1.79), 14.11 (± 3.54), and 19.52 (± 6.04) hr•mcg/mL, respectively.

There was also a lack of dose proportionality in acyclovir C_{max} and AUC after the multiple-dose administration of 250 mg, 500 mg, and 1 gram of VALTREX administered 4 times daily for 11 days in parallel groups of 8 healthy volunteers. The mean C_{max} (± SD) was 2.11 (± 0.33), 3.69 (± 0.87), and 4.96 (± 0.64) mcg/mL, respectively, and the mean AUC (± SD) was 5.66 (± 1.09), 9.88 (± 2.01), and 15.70 (± 2.27) hr•mcg/mL, respectively.

There is no accumulation of acyclovir after the administration of valacyclovir at the recommended dosage regimens in healthy volunteers with normal renal function.

Distribution: The binding of valacyclovir to human plasma proteins ranged from 13.5% to 17.9%.

Metabolism: After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract. Valacyclovir is converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. Acyclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valacyclovir nor acyclovir is metabolized by cytochrome P450 enzymes. Plasma concentrations of unconverted valacyclovir are low and transient, generally becoming non-quantifiable by 3 hours after administration. Peak plasma valacyclovir concentrations are generally less than 0.5 mcg/mL at all doses. After single-dose administration of 1 gram of VALTREX, average plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 mcg/mL in patients with hepatic dysfunction, renal insufficiency, and in healthy volunteers who received concomitant cimetidine and probenecid, respectively.

Elimination: The pharmacokinetic disposition of acyclovir delivered by valacyclovir is consistent with previous experience from intravenous and oral acyclovir. Following the oral administration of a single 1-gram dose of radiolabeled valacyclovir to 4 healthy subjects, 45.60% and 47.12% of administered radioactivity was recovered in urine and feces over 96 hours, respectively. Acyclovir accounted for 88.60% of the radioactivity excreted in the urine. Renal clearance of acyclovir following the administration of a single 1-gram dose of VALTREX to 12 healthy volunteers was approximately 255 ± 86 mL/min which represents 41.9% of total acyclovir apparent plasma clearance.

The plasma elimination half-life of acyclovir typically averaged 2.5 to 3.3 hours in all studies of VALTREX in volunteers with normal renal function.

End-Stage Renal Disease (ESRD): Following administration of VALTREX to volunteers with ESRD, the average acyclovir half-life is approximately 14 hours. During hemodialysis, the acyclovir half-life is approximately 4 hours. Approximately one third of acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session. Apparent plasma clearance of acyclovir in dialysis patients was 86.3 ± 21.3 mL/min/1.73 m^2, compared to 679.16 ± 162.76 mL/min/1.73 m^2 in healthy volunteers.

Reduction in dosage is recommended in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Geriatrics: After single-dose administration of 1 gram of VALTREX in healthy geriatric volunteers, the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 2.91 ± 0.63 hours in healthy volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTREX in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics: Valacyclovir pharmacokinetics have not been evaluated in pediatric patients.

Liver Disease: Administration of VALTREX to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate but not the extent of conversion of valacyclovir to acyclovir is reduced, and the acyclovir half-life is not affected. Dosage modification is not recommended for patients with cirrhosis.

HIV Disease: In 9 patients with advanced HIV disease (CD4 cell counts <150 cells/mm^3) who received VALTREX at a dosage of 1 gram 4 times daily for 30 days, the pharmacokinetics of valacyclovir and acyclovir were not different from that observed in healthy volunteers (see WARNINGS).

Drug Interactions: The pharmacokinetics of digoxin was not affected by coadministration of VALTREX 1 gram 3 times daily, and the pharmacokinetics of acyclovir after a single dose of VALTREX (1 gram) was unchanged by coadministration of digoxin (2 doses of 0.75 mg), single doses of antacids (Al^{3+} or Mg^{++}), or multiple doses of thiazide diuretics. Acyclovir C_{max} and AUC following a single dose of VALTREX (1 gram) increased by 8% and 32%, respectively, after a single dose of cimetidine (800 mg), or by 22% and 49%, respectively, after probenecid (1 gram), or by 30% and 78%, respectively, after a combination of cimetidine and probenecid, primarily due to a reduction in renal clearance of acyclovir. These effects are not considered to be of clinical significance in subjects with normal renal function. Therefore, no dosage adjustment is recommended when VALTREX is coadministered with digoxin, antacids, thiazide diuretics, cimetidine, or probenecid in subjects with normal renal function.

Clinical Trials:

Herpes Zoster Infections: Two randomized double-blind clinical trials in immunocompetent adults with localized herpes zoster were conducted. VALTREX was compared to placebo in patients less than 50 years of age, and to ZOVIRAX in patients greater than 50 years of age. All patients were treated within 72 hours of appearance of zoster rash. In patients less than 50 years of age, the median time to cessation of new lesion formation was 2 days for those treated with VALTREX compared to 3 days for those treated with placebo. In patients greater than 50 years of age, the median time to cessation of new lesions was 3 days in patients treated with either VALTREX or ZOVIRAX. In patients less than 50 years of age, no difference was found with respect to the duration of pain after healing (post-herpetic neuralgia) between the recipients of

VALTREX and placebo. In patients greater than 50 years of age, among the 83% who reported pain after healing (post-herpetic neuralgia), the median duration of pain after healing [95% confidence interval] in days was: 40 [31, 51], 43 [36, 55], and 59 [41, 77] for 7-day VALTREX, 14-day VALTREX, and 7-day ZOVIRAX, respectively.

Genital Herpes Infections: Initial Episode: Six hundred and forty-three immunocompetent adults with first episode genital herpes who presented within 72 hours of symptom onset were randomized in a double-blind trial to receive 10 days of VALTREX 1 gram twice daily (n = 323) or ZOVIRAX 200 mg 5 times a day (n = 320). For both treatment groups: the median time to lesion healing was 9 days, the median time to cessation of pain was 5 days, the median time to cessation of viral shedding was 3 days.

Recurrent Episodes: Three double-blind trials (2 of them placebo-controlled) in immunocompetent adults with recurrent genital herpes were conducted. Patients self initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

In 1 study, patients were randomized to receive 5 days of treatment with either VALTREX 500 mg twice daily (n = 360) or placebo (n = 259). The median time to lesion healing was 4 days in the group receiving VALTREX 500 mg versus 6 days in the placebo group, and the median time to cessation of viral shedding in patients with at least 1 positive culture (42% of the overall study population) was 2 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. The median time to cessation of pain was 3 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. Results supporting efficacy were replicated in a second trial.

In a third study, patients were randomized to receive VALTREX 500 mg twice daily for 5 days (n = 398) or VALTREX 500 mg twice daily for 3 days (and matching placebo twice daily for 2 additional days) (n = 402). The median time to lesion healing was about 4½ days in both treatment groups. The median time to cessation of pain was about 3 days in both treatment groups.

Suppressive Therapy: Two clinical studies were conducted, one in immunocompetent adults and one in HIV-infected adults.

A double-blind, 12-month, placebo- and active-controlled study enrolled immunocompetent adults with a history of 6 or more recurrences per year. Outcomes for the overall study population are shown in Table 49.

Table 49. Proportions of Patients Recurrence Free at 6 and 12 Months

Treatment Arm	6 Months			12 Months		
	VALTREX 1 gram q.d. (n = 269)	ZOVIRAX 400 mg b.i.d. (n = 267)	Placebo (n = 134)	VALTREX 1 gram q.d. (n = 269)	ZOVIRAX 400 mg b.i.d. (n = 267)	Placebo (n = 134)
Recurrence free (%)	55	54	7	34	34	4
Recurrences (%)	35	36	83	46	46	85
Unknowns (%) *	10	10	10	19	19	10

*Includes lost to follow-up, discontinuations due to adverse events, and consent withdrawn.

Subjects with 9 or fewer recurrences per year showed comparable results with VALTREX 500 mg once daily.

In a second study, 293 HIV-infected adults on stable antiretroviral therapy with a history of 4 or more recurrences of ano-genital herpes per year were randomized to receive either VALTREX 500 mg twice daily (n = 194) or matching placebo (n = 99) for 6 months. The median duration of recurrent genital herpes in enrolled subjects was 8 years, and the median number of recurrences in the year prior to enrollment was 5. Overall, the median prestudy HIV-1 RNA was 2.6 $\log_{10}$ copies/mL. Among patients who received VALTREX, the prestudy median CD4 cell count was 336 cells/mm^3; 11% had <100 cells/mm^3, 16% had 100 to 199 cells/mm^3, 42% had 200 to 499 cells/mm^3, and 31% had ≥500 cells/mm^3. Outcomes for the overall study population are shown in Table 50.

Table 50. Recurrence Rates in HIV-Infected Adults at 6 Months

Treatment Arm	VALTREX 500 mg b.i.d. (n = 194)	Placebo (n = 99)
Recurrence free	65%	26%
Recurrences	17%	57%
Unknowns*	18%	17%

*Includes lost to follow-up, discontinuations due to adverse events, and consent withdrawn.

Cold Sores (Herpes Labialis): Two double-blind, placebo-controlled clinical trials were conducted in 1,856 healthy adults and adolescents (≥12 years old) with a history of recurrent cold sores. Patients self initiated therapy at the earliest symptoms and prior to any signs of a cold sore. The majority of patients initiated treatment within 2 hours of onset of symptoms. Patients were randomized to VALTREX 2 grams twice daily on Day 1 followed by placebo on Day 2, VALTREX 2 grams twice daily on Day 1 followed by 1 gram twice daily on Day 2, or placebo on Days 1 and 2.

The mean duration of cold sore episodes was about 1 day shorter in treated subjects as compared to placebo. The 2-day regimen did not offer additional benefit over the 1-day regimen.

No significant difference was observed between subjects receiving VALTREX or placebo in the prevention of progression of cold sore lesions beyond the papular stage.

INDICATIONS AND USAGE

Herpes Zoster: VALTREX is indicated for the treatment of herpes zoster (shingles).

Genital Herpes: VALTREX is indicated for the treatment or suppression of genital herpes in immunocompetent individuals and for the suppression of recurrent genital herpes in HIV-infected individuals.

Cold Sores (Herpes Labialis): VALTREX is indicated for the treatment of cold sores (herpes labialis).

CONTRAINDICATIONS

VALTREX is contraindicated in patients with a known hypersensitivity or intolerance to valacyclovir, acyclovir, or any component of the formulation.

WARNINGS

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease and also in allogeneic bone marrow transplant and renal transplant recipients participating in clinical trials of VALTREX at doses of 8 grams per day.

PRECAUTIONS

Dosage reduction is recommended when administering VALTREX to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Acute renal failure and central nervous system symptoms have been reported in patients with underlying renal disease who have received inappropriately high doses of VALTREX for their level of renal function. Similar caution should be exercised when administering VALTREX to geriatric patients (see Geriatric Use) and patients receiving potentially nephrotoxic agents.

Given the dosage recommendations for treatment of cold sores, special attention should be paid when prescribing VALTREX for cold sores in patients who are elderly or who have impaired renal function (see DOSAGE AND ADMINISTRATION and Geriatric Use). Treatment should not exceed 1 day (2 doses of 2 grams in 24 hours). Therapy beyond 1 day does not provide additional clinical benefit.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of VALTREX have not been established in immunocompromised patients other than for the suppression of genital herpes in HIV-infected patients. The

safety and efficacy of VALTREX for suppression of recurrent genital herpes in patients with advanced HIV disease (CD4 cell count <100 cells/mm^3) have not been established. The efficacy of VALTREX for the treatment of genital herpes in HIV-infected patients has not been established. The safety and efficacy of VALTREX have not been established for the treatment of disseminated herpes zoster.

Information for Patients:

Herpes Zoster: There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes: Patients should be informed that VALTREX is not a cure for genital herpes. There are no data evaluating whether VALTREX will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

There are no data on the effectiveness of treatment initiated more than 72 hours after the onset of signs and symptoms of a first episode of genital herpes or more than 24 hours of the onset of signs and symptoms of a recurrent episode.

There are no data on the safety or effectiveness of chronic suppressive therapy of more than 1 year's duration. There are no data on the safety or effectiveness of chronic suppressive therapy of more than 6 months' duration in HIV-infected patients.

Cold Sores (Herpes Labialis): Patients should be advised to initiate treatment at the earliest symptom of a cold sore (e.g., tingling, itching, or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer). Patients should be instructed that treatment for cold sores should not exceed 1 day (2 doses) and that their doses should be taken about 12 hours apart. Patients should be informed that VALTREX is not a cure for cold sores (herpes labialis).

Drug Interactions: See CLINICAL PHARMACOLOGY: Pharmacokinetics.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to the steady-state acyclovir AUC observed in humans treated with 1 gram VALTREX given orally 3 times a day to treat herpes zoster. Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Valacyclovir was noncarcinogenic in lifetime carcinogenicity bioassays at single daily doses (gavage) of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tumors between treated and control animals, nor did valacyclovir shorten the latency of tumors. Plasma concentrations of acyclovir

were equivalent to human levels in the mouse bioassay and 1.4 to 2.3 times human levels in the rat bioassay.

Valacyclovir was tested in 5 genetic toxicity assays. An Ames assay was negative in the absence or presence of metabolic activation. Also negative were an in vitro cytogenetic study with human lymphocytes and a rat cytogenetic study at a single oral dose of 3,000 mg/kg (8 to 9 times human plasma levels).

In the mouse lymphoma assay, valacyclovir was not mutagenic in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was mutagenic.

Valacyclovir was not mutagenic in a mouse micronucleus assay at 250 mg/kg but positive at 500 mg/kg (acyclovir concentrations 26 to 51 times human plasma levels).

Valacyclovir did not impair fertility or reproduction in rats at 200 mg/kg/day (6 times human plasma levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Valacyclovir was not teratogenic in rats or rabbits given 400 mg/kg (which results in exposures of 10 and 7 times human plasma levels, respectively) during the period of major organogenesis.

There are no adequate and well-controlled studies of VALTREX or ZOVIRAX in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. VALTREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: There is no experience with VALTREX. However, acyclovir concentrations have been documented in breast milk in 2 women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. VALTREX should be administered to a nursing mother with caution and only when indicated.

Pediatric Use: Safety and effectiveness of VALTREX in pre-pubertal pediatric patients have not been established.

Geriatric Use: Of the total number of subjects in clinical studies of VALTREX, 889 were 65 and over, and 350 were 75 and over. In a clinical study of herpes zoster, the duration of pain after healing (post-herpetic neuralgia) was longer in patients 65 and older compared with younger adults. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during

clinical practice, agitation, hallucinations, confusion, delirium, and encephalopathy were reported more frequently in elderly patients (see CLINICAL PHARMACOLOGY, ADVERSE REACTIONS: Observed During Clinical Practice, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Frequently reported adverse events in clinical trials of VALTREX are listed in Tables 51 and 52.

Table 51. Incidence (%) of Adverse Events in Herpes Zoster Study Populations

Adverse Event	VALTREX 1 gram t.i.d. (n = 967)	Placebo (n = 195)
Nausea	15%	8%
Headache	14%	12%
Vomiting	6%	3%
Dizziness	3%	2%
Abdominal pain	3%	2%

Table 52. Incidence (%) of Adverse Events in Genital Herpes Study Populations

	Genital Herpes Treatment			Genital Herpes Suppression		
Adverse Event	VALTREX 1 gram b.i.d. (n = 1194)	VALTREX 500 mg b.i.d. (n = 1159)	Placebo (n = 439)	VALTREX 1 gram q.d. (n = 269)	VALTREX 500 mg q.d. (n = 266)	Placebo (n = 134)
Nausea	6%	5%	8%	11%	11%	8%
Headache	16%	15%	14%	35%	38%	34%
Vomiting	1%	<1%	<1%	3%	3%	2%
Dizziness	3%	2%	3%	4%	2%	1%
Abdominal pain	2%	1%	3%	11%	9%	6%
Dysmenorrhea	<1%	<1%	1%	8%	5%	4%
Arthralgia	<1%	<1%	<1%	6%	5%	4%
Depression	1%	0%	<1%	7%	5%	5%

In clinical studies for the treatment of cold sores, the adverse events reported by patients receiving VALTREX (n = 609) or placebo (n = 609) included headache (VALTREX 14%, placebo 10%) and dizziness (VALTREX 2%, placebo 1%).

Laboratory abnormalities reported in clinical trials of VALTREX are listed in Table 53.

Table 53. Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations

Laboratory Abnormality	Herpes Zoster		Genital Herpes Treatment			Genital Herpes Suppression		
	VALTREX 1 gram t.i.d.	PBO	VALTREX 1 gram b.i.d.	VALTREX 500 mg b.i.d.	PBO	VALTREX 1 gram q.d.	VALTREX 500 mg q.d.	PBO
Hemoglobin (<0.8 x LLN)	0.8%	0%	0.3%	0.2%	0%	0%	0.8%	0.8%
White blood cells (<0.75 x LLN)	1.3%	0.6%	0.7%	0.6%	0.2%	0.7%	0.8%	1.5%
Platelet count (<100,000/mm^3)	1.0%	1.2%	0.3%	0.1%	0.7%	0.4%	1.1%	1.5%
AST (SGOT) (>2 x ULN)	1.0%	0%	1.0%	*	0.5%	4.1%	3.8%	3.0%
Serum creatinine (>1.5 x ULN)	0.2%	0%	0.7%	0%	0%	0%	0%	0%

*Data were not collected prospectively
LLN = Lower limit of normal
ULN = Upper limit of normal

Suppression of Genital Herpes in HIV-Infected Patients: In HIV-infected patients, frequently reported adverse events for VALTREX (500 mg twice daily; n = 194, median days on therapy = 172) and placebo (n = 99, median days on therapy = 59), respectively, included headache (13% vs. 8%), fatigue (8% vs. 5%), and rash (8% vs. 1%). Post-randomization laboratory abnormalities that were reported more frequently in valacyclovir subjects versus placebo included elevated alkaline phosphatase (4% vs. 2%), elevated ALT (14% vs. 10%), elevated AST (16% vs. 11%), decreased neutrophil counts (18% vs. 10%), and decreased platelet counts (3% vs. 0%).

In clinical studies for the treatment of cold sores, the frequencies of abnormal ALT (>2 x ULN) were 1.8% for patients receiving VALTREX compared with 0.8% for placebo. Other laboratory abnormalities (hemoglobin, white blood cells, alkaline phosphatase, and serum creatinine) occurred with similar frequencies in the 2 groups.

Observed During Clinical Practice: The following events have been identified during post-approval use of VALTREX in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to VALTREX, or a combination of these factors.

General: Facial edema, hypertension, tachycardia.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria.

CNS Symptoms: Aggressive behavior; agitation; ataxia; coma; confusion; decreased consciousness; dysarthria; encephalopathy; mania; and psychosis, including auditory and visual hallucinations; seizures (see PRECAUTIONS).

Eye: Visual abnormalities.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Elevated creatinine, renal failure.

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS.

Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

Renal Impairment: Renal failure and CNS symptoms have been reported in patients with renal impairment who received VALTREX or acyclovir at greater than the recommended dose. **Dose reduction is recommended in this patient population (see DOSAGE AND ADMINISTRATION).**

OVERDOSAGE

Caution should be exercised to prevent inadvertent overdose (see PRECAUTIONS). Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

VALTREX Caplets may be given without regard to meals.

Herpes Zoster: The recommended dosage of VALTREX for the treatment of herpes zoster is 1 gram orally 3 times daily for 7 days. Therapy should be initiated at the earliest sign or symptom of herpes zoster and is most effective when started within 48 hours of the onset of zoster rash. No data are available on efficacy of treatment started greater than 72 hours after rash onset.

Genital Herpes: ***Initial Episodes:*** The recommended dosage of VALTREX for treatment of initial genital herpes is 1 gram twice daily for 10 days.

There are no data on the effectiveness of treatment with VALTREX when initiated more than 72 hours after the onset of signs and symptoms. Therapy was most effective when administered within 48 hours of the onset of signs and symptoms.

Recurrent Episodes: The recommended dosage of VALTREX for the treatment of recurrent genital herpes is 500 mg twice daily for 3 days.

If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode. There are no data on the effectiveness of treatment with VALTREX when initiated more than 24 hours after the onset of signs or symptoms.

Suppressive Therapy: The recommended dosage of VALTREX for chronic suppressive therapy of recurrent genital herpes is 1 gram once daily. In patients with a history of 9 or fewer recurrences per year, an alternative dose is 500 mg once daily. The safety and efficacy of therapy with VALTREX beyond 1 year have not been established.

In HIV-infected patients with CD4 cell count ≥100 cells/mm^3, the recommended dosage of VALTREX for chronic suppressive therapy of recurrent genital herpes is 500 mg twice daily. The safety and efficacy of therapy with VALTREX beyond 6 months in patients with HIV infection have not been established.

Cold Sores (Herpes Labialis): The recommended dosage of VALTREX for the treatment of cold sores is 2 grams twice daily for 1 day taken about 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (e.g., papule, vesicle, or ulcer).

Patients with Acute or Chronic Renal Impairment: In patients with reduced renal function, reduction in dosage is recommended (see Table 54).

Table 54. Dosages for Patients with Renal Impairment

Indications	Normal Dosage Regimen (Creatinine Clearance ≥50)	Creatinine Clearance (mL/min)		
		30-49	10-29	<10
Herpes zoster	**1 gram every 8 hours**	**1 gram every 12 hours**	**1 gram every 24 hours**	**500 mg every 24 hours**
Genital herpes				
Initial treatment	1 gram every 12 hours	no reduction	1 gram every 24 hours	500 mg every 24 hours
Recurrent episodes	500 mg every 12 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Suppressive therapy	1 gram every 24 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Suppressive therapy	500 mg every 24 hours	no reduction	500 mg every 48 hours	500 mg every 48 hours
Suppressive therapy in HIV patients	500 mg every 12 hours	no reduction	500 mg every 24 hours	500 mg every 24 hours
Herpes labialis (cold sores) **Do not exceed 1 day of treatment.**	Two 2-gram doses taken about 12 hours apart	Two 1-gram doses taken about 12 hours apart	Two 500-mg doses taken about 12 hours apart	500-mg single dose

Hemodialysis: During hemodialysis, the half-life of acyclovir after administration of VALTREX is approximately 4 hours. About one third of acyclovir in the body is removed by dialysis during a 4-hour hemodialysis session. Patients requiring hemodialysis should receive the recommended dose of VALTREX after hemodialysis.

Peritoneal Dialysis: There is no information specific to administration of VALTREX in patients receiving peritoneal dialysis. The effect of chronic ambulatory peritoneal dialysis (CAPD) and continuous arteriovenous hemofiltration/dialysis (CAVHD) on acyclovir pharmacokinetics has been studied. The removal of acyclovir after CAPD and CAVHD is less pronounced than with hemodialysis, and the pharmacokinetic parameters closely resemble those observed in patients with ESRD not receiving hemodialysis. Therefore, supplemental doses of VALTREX should not be required following CAPD or CAVHD.

HOW SUPPLIED

VALTREX Caplets (blue, film-coated, capsule-shaped tablets) containing valacyclovir hydrochloride equivalent to 500 mg valacyclovir and printed with "VALTREX 500 mg." Bottle of 30 (NDC 0173-0933-08) and unit dose pack of 100 (NDC 0173-0933-56).

VALTREX Caplets (blue, film-coated, capsule-shaped tablets) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir and printed with "VALTREX 1 gram." Bottle of 21 (NDC 0173-0565-02).

Store at 15° to 25°C (59° to 77°F).

GlaxoSmithKline

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