Official Title:	Zoster Eye Disease Study (ZEDS): A multi-center, randomized, double-masked, placebo-controlled clinical trial of suppressive valacyclovir for one year in immunocompetent study participants with an episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to Herpes Zoster Ophthalmicus (HZO) in the year prior to enrollment.
NCT Number:	NCT03134196
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Zoster Eye Disease Study (ZEDS):

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Protocol Identifying Number: 16-00463

Principal Investigator: Elisabeth Cohen, MD

Funded by: The National Eye Institute

Version Number: 3.0

March 25, 2020

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LIST OF ABBREVIATIONS

AE	Adverse event
APT	Acyclovir Prevention Trial
CC	Coordinating Center
CMP	Clinical Monitoring Plan
CCT	Central Corneal Thickness
CDC	Centers for Disease Control
CIRB	Central IRB
CNS	Central Nervous System
CRF	Case Report Form
CTSA	Clinical Translational Science Award
DDC	Drug Distribution Center
DSMC	Data and Safety Monitoring Committee
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
HEDS	Herpetic Eye Disease Study
HSV	Herpes Simplex Virus
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HUS	Hemolytic Uremic Syndrome
HZ	Herpes Zoster
HZO	Herpes Zoster Ophthalmicus
IC50	Inhibitory Concentration to Reduce by 50%
ICF	Informed Consent Form

IOP	Intraocular Pressure
IRB	Institutional Review Board
IXRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Operations and Procedures
NEI	National Eye Institute
NYULMC	NYU Langone Medical Center
NYUSoM	NYU School of Medicine
PCC	Participating Clinical Center
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PHN	Postherpetic Neuralgia
PI	Principal Investigator
QOL	Quality of Life
RCT	Randomized Controlled (Clinical) Trial
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TMF	Trial Master File
TTP	Thrombotic Thrombocytopenic Purpura
V1 and V2	Cranial Nerve five (Trigeminal Nerve), first and second division
VZV	Varicella Zoster Virus
ZBPI	Zoster Brief Pain Inventory
ZVL	Zoster Vaccine Live
ZEDS	Zoster Eye Disease Study

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6 (R2) Guideline for Good Clinical Practice, the U.S. Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), the Code of Federal Regulations applicable to clinical studies (21 CFR 312 – Investigational New Drug Application, 21 CFR 50 – Protection of Human Subjects and 21 CFR 54 – Financial Disclosure by Clinical Investigator, 21 CFR 56 – Institutional Review Boards), and the National Eye Institute Terms of Award. The Principal Investigator at the Participating Clinical Site (PCC) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

PCC Principal Investigator (PI): _____

PCC PI Signature: _____ Date: _____

PROTOCOL SUMMARY

Title: Zoster Eye Disease Study (ZEDS): A multi-center, randomized, double-masked, placebo-controlled clinical trial of valacyclovir for one year in immunocompetent study participants with an episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to Herpes Zoster Ophthalmicus (HZO) in the year prior to enrollment.

Précis: The study is a double-masked, multi-center, randomized clinical trial (RCT) that will enroll immunocompetent study participants age 18 years and older who have HZO diagnosed at variable times in the past, with an episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO in the year prior to enrollment. Eligible study participants will be randomized in a 1:1 ratio to long-term suppressive treatment with oral valacyclovir 1000 mg daily or placebo for one year, and followed every 3 months for a total of 18 months, to determine outcomes of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis and severity and duration of postherpetic neuralgia during 12 months of treatment and for 6 months following treatment discontinuation. Participants will be randomized within center in four strata, defined by age at onset of HZO (less than 60 years or 60 years and greater) and by recent onset or chronic HZO (recent onset defined as HZO diagnosed within 6 months of enrollment/randomization, or chronic defined as HZO diagnosed 6 months or more prior to enrollment/randomization).

Objectives: To evaluate whether or not prolonged suppressive oral antiviral treatment with valacyclovir reduces complications of HZO including new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis and/or postherpetic neuralgia compared to placebo.

Endpoint: The primary endpoint is the time to first occurrence of new or worsening episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, during the twelve months of treatment, requiring pre-specified treatment changes. The primary endpoint is compared for participants randomized to study medication or placebo

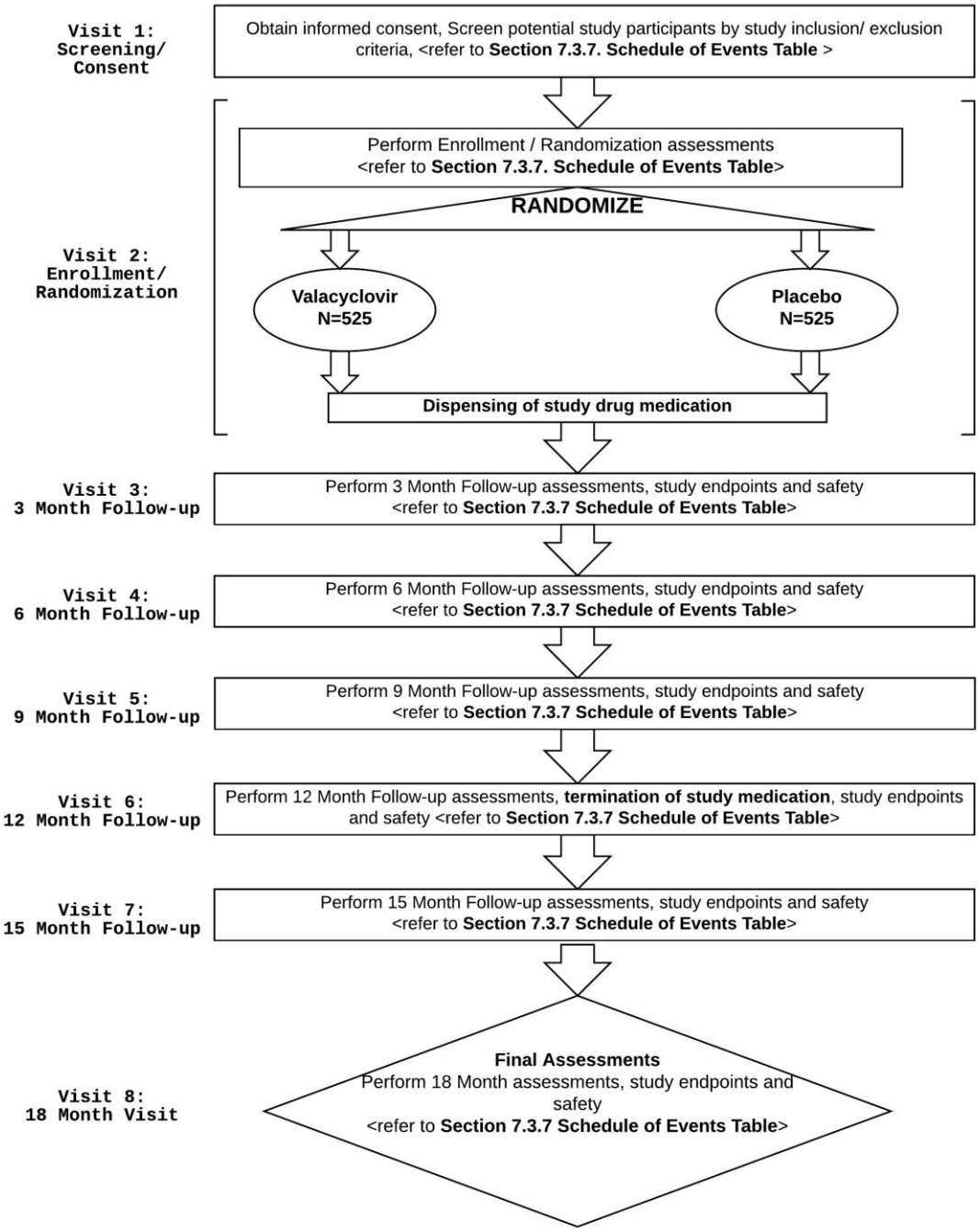
Population: Immunocompetent participants age 18 years or older with a past diagnosis of HZO that included:

- Cranial nerve V1 or V2 involvement with history of typical rash
- Medically documented episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO in the year prior to enrollment.

Phase: NIH defined Phase 3 (FDA defined Phase 4)

Number of Participating Clinical Centers (PCC)	Approximately 70-80 PCCs
Description of Study Agent:	Valacyclovir: two 500 mg pills daily Placebo: encapsulated matching placebo
Study Duration:	Estimated 8 years: 12 months treatment and additional follow-up period up to 6 months.
Participant Duration:	Up to 18 months (12 months receiving study medication)

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Herpes Zoster Ophthalmicus (HZO) is associated with unilateral acute and chronic eye disease and pain, with potential complications that can significantly impair functioning and reduce quality of life (QOL) among millions of Americans, especially older adults. Although there is considerable consensus on treatment of acute HZO in immunocompetent adults, there is no standard approach to treatment of HZO sequelae such as ocular disease and postherpetic neuralgia (PHN), a severely debilitating chronic pain syndrome**.** Several factors call for evaluating long-term suppressive antivirals to prevent HZO complications in a randomized controlled trial: recent discoveries about the infectious pathogenesis of complications of herpes zoster (HZ) and HZO; the significant benefit of suppressive antivirals in reducing recurrent herpes simplex virus (HSV) stromal keratitis; and evidence of comparable, marked benefit of suppressive antiviral treatment of chronic HZO and HSV in a retrospective study (1-4). HZO and HSV eye disease have some clinical similarities in that primary infection (with these different herpes viruses) is followed by latency, and recurrent infection is frequently associated with chronic and/or recurrent eye disease, both of which can lead to loss of vision. HZ results from acute reactivation of latent varicella zoster virus (VZV). It was confirmed only recently, however, that complications of HZ may be associated with chronic or recurrent active infection rather than manifestations of inflammatory, immune, neuropathic and vascular sequelae of infection. For example, a 1995 study showed that late dendriform epithelial keratitis lesions are often polymerase chain reaction (PCR) positive for VZV, and this was confirmed by a larger series in 2010 (2, 3). Dendriform epithelial keratitis responds to topical and systemic antiviral treatment: further evidence it is caused by active VZV infection (3, 5). There is also evidence associating chronic, active VZV infection with PHN, vasculopathy after HZ resulting in potentially fatal strokes, and giant cell (temporal) arteritis (6-9). The concept that persistent active infection results in chronic HZO has generated interest and debate among experts. A 2012 editorial in Archives of Ophthalmology suggested that, "…although stromal keratitis or uveitis may not represent active viral infection, clinicians may question whether subclinical or intermittent viral shedding may help to perpetuate destructive, inflammatory, anterior segment disease in HZO" (10). Corneal changes that result in visual loss from VZV keratitis are estimated by corneal specialists to occur in 20-40% of cases. In a recent report, the mean number of recurrences of HZO was decreased with antiviral treatment from 3.4 episodes per year to 2.1 episodes per year ($p<0.05$) suggesting that prolonged long-term antivirals at the higher dose to be used in the Zoster Eye Disease Study (ZEDS) trial may reduce morbidity, including visual loss, associated with chronic HZO, and could significantly reduce the disease burden for patients and the costs to society (1).

ZEDS seeks to answer this question for HZO caused by VZV much as the Herpetic Eye Disease Study (HEDS) Acyclovir Prevention Trial (APT) did for HSV ocular disease, with a double-masked, placebo-controlled, multi-center randomized controlled trial (RCT) in immunocompetent study participants age 18 and older with a past diagnosis of HZO and an episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis diagnosed within the past year (4). In HEDS, prolonged suppressive antiviral treatment was most beneficial in preventing recurrence of stromal keratitis, suggesting that active viral infection is an important factor contributing to stromal keratitis, although the mechanism is not understood (4). The ZEDS design is analogous to the HEDS design. Study participants with HZO will be randomized in a double-masked, placebo-controlled RCT to 1 year of suppressive antiviral treatment with oral valacyclovir or placebo, with follow-up every 3 months for a total of 18 months, to compare the rates of new or worsening dendriform

epithelial keratitis, stromal keratitis, endothelial keratitis, or iritis and severity and duration of PHN by 12 months of treatment and 6 months after treatment.

Evidence of Chronic Active VZV Infection after HZ and HZO

The rationale for the study includes the increasing body of evidence that chronic active VZV infection occurs after HZ and contributes to complications, including PHN, stroke, and temporal arteritis, in addition to dendriform epithelial keratitis and uveitis (11-14). VZV DNA has been found to persist in the saliva of 67% (21/32) of persons age 60 and older with a history of HZ up to 12 years after disease onset (15). In HZO, evidence from PCR testing shows that active VZV infection contributes to late dendriform epithelial keratitis, a characteristic manifestation of HZO with median occurrence 5 months after HZO onset, and uveitis (2, 3, 14). The finding of VZV DNA in blood mononuclear cells of HZ patients with PHN, in the arteries of patients with zoster-related strokes, and, most recently, in temporal arteries of patients with possible and proven giant cell arteritis, is helping to raise awareness of the devastating consequences of chronic active VZV infection, the importance of accurate diagnosis, and the potential for improved antiviral treatment of these conditions. Given evidence that active VZV infection contributes to PHN, and the lack of effective and well tolerated treatment for PHN, it is important to study the efficacy of suppressive antiviral treatment for this extremely painful and debilitating condition that negatively impacts QOL, especially in the elderly, by prospectively collecting data regarding PHN severity and treatment. The results with regard to PHN may be generalizable to HZ in other anatomic locations; PHN lasts more than a year in nearly half of patients older than age 70, reduces QOL in direct proportion to the severity and duration of pain, and more than quadruples the one year costs of the disease. In 2014, HZ was reported as a risk factor for myocardial infarction in addition to cerebrovascular disease (16-18). An editorial in Clinical Infectious Diseases concludes, “The growing awareness of the role of VZV in vascular disease promises to lead to clinical trials to assess the benefit of antiviral therapy.” (19)

HEDS: Oral Antivirals to Reduce Recurrent Ocular HSV Disease

The HEDS APT examined long-term use of oral acyclovir to prevent recurrent HSV disease, and found a 45% reduction (95% CI 0.41-0.75, p<0.001) in recurrent ocular disease over 1 year (4). On the basis of this landmark study, recommended care for HSV eye disease changed to include prolonged suppressive antiviral treatment. In HEDS, although high-dose oral antiviral therapy for 10 weeks was not effective in treating stromal keratitis, prolonged suppressive antiviral treatment for 1 year in the HEDS APT was most beneficial in preventing recurrence of this form of disease in study participants who had a history of stromal keratitis, reducing it from 28% to 14% (95% CI 0.29-0.80, p=0.005) (4, 20). The efficacy of suppressive antiviral treatment in preventing stromal keratitis and lack of efficacy of high-dose antiviral treatment for stromal keratitis are consistent with greater efficacy of prolonged suppressive antiviral treatment in general. The clinical benefit was greater for stromal keratitis than dendritic keratitis because stromal keratitis results in more scarring and permanent damage than superficial epithelial (dendritic) keratitis (4). There is no direct evidence that viral reactivation causes HSV stromal keratitis, yet HEDS showed that suppression of HSV reduces the rate of recurrence of HSV stromal keratitis. There is an absence of direct evidence that viral replication contributes to either HZO or HSV stromal keratitis.

Prolonged suppressive antiviral treatment has improved outcomes of ocular HSV. The HEDS trial results were observed in a real-world setting. A retrospective community-based cohort study investigating the impact of prophylactic antiviral treatment for HSV keratitis, published in 2010, concluded that patients were significantly less likely to have recurrent HSV epithelial keratitis and stromal keratitis on prolonged suppressive treatment (21).

We hypothesize that prolonged suppressive valacyclovir treatment will reduce the occurrence of stromal keratitis and dendriform epithelial keratitis in HZO patients. HSV stromal keratitis is primarily immune-mediated; while the trigger or mechanism of recurrent inflammation is uncertain, there is strong clinical evidence that suppressive antiviral treatment decreases its frequency (22). HSV and VZV stromal keratitis are analogous diseases, and our aim is to determine whether VZV stromal keratitis can be reduced by suppressive antiviral treatment in a similar fashion to HSV stromal keratitis. If results of the trial are similar with regard to antiviral suppression reducing infectious and inflammatory chronic ocular disease in HZO, the benefits to patients will be significant as this therapy is adopted as standard of care.

Preliminary Studies

In preparation for this trial, study leaders conducted and published a retrospective study of over 100 HZO patients treated at a tertiary referral center and found that late dendriform epithelial keratitis occurred more often in patients who were under age 60 at time of HZO onset compared with those age 60 or older at onset (36% vs. 17%, p=0.03) (23). Younger patients averaged 3.2 episodes of recurrent inflammation, and older patients 1.5 during follow-up (p=0.01). In both groups, over 80% of patients remained on topical corticosteroids three years after referral. Complications including PHN, neurotrophic keratitis and secondary infected corneal ulcers were all significantly more common in older-onset patients (38% for those age 60 or older at onset vs. 8% for those under age 60 at onset, p=0.001, 31% v. 9% p=0.005, and 17% v. 3%, p=0.04, respectively) (23).

Current Practice Patterns and Opinions

A survey of 100 corneal specialists was also conducted in preparation for this study; over 85% of specialists reported treating cases of chronic or recurrent HZO in the preceding year. They reported prescribing oral antivirals most often for 7-14 days (37%), while some used them for a year or longer (15%), and others as long as patients were on topical corticosteroids (15%) (24).

Suppressive Antivirals Preferred by Cornea Specialists

The choice of antiviral regimen for study was based in part on an electronic survey conducted in preparation for the project (25). This survey was sent to ophthalmologists, including leaders of cornea fellowship training programs and/or cornea subspecialty societies, and to those with special interest in cornea, as indicated by participation in Kera-net, the official forum and listserv of the Cornea Society. The 171 respondents included 69% (46/67) of the cornea leaders surveyed. Valacyclovir 500 mg bid was the preferred antiviral regimen (36%), followed by acyclovir 800 mg bid (33%), valacyclovir 1000 mg daily (28%), and finally, famciclovir 250 mg bid (4%). Further, over 60% of the survey respondents were definitely interested in participating in the study.

Pilot Studies

Several recent studies provide important lines of evidence that serve as pilot data and inform aspects of the trial design. An observational study from an Ocular Immunology and Uveitis Service at an Italian referral center treating patients with chronic HZO, published in 2014, looked at patients who were routinely prescribed suppressive antiviral treatment. The study found that in patients who were referred an average of 3 years after disease onset, prolonged treatment with antiviral valacyclovir 500 mg daily or acyclovir 400 mg bid reduced the overall number of recurrences to 2.1 per year, compared to 3.4 episodes without antiviral treatment, a 35% reduction (p<.05) (1). In this study, the same suppressive antiviral treatment of HSV keratitis reduced recurrences to 2.3 from 3.8, a 39% reduction (p<0.05). The percent reduction of recurrent HSV (39%) was comparable to the percent reduction of HSV (45%) in HEDS, and comparable to the reduction of recurrent

inflammation in HZO (35%) in this observational study. This pilot data support the projected risk reduction (30%) postulated for the ZEDS RCT. This observational study also provides data on the relative prevalence of types of recurrences: inflammation recurred in 51% of HZO patients followed for an average of 2 years (range 1-6 years), including stromal keratitis (20%) followed by anterior uveitis (13.3%), keratouveitis (8.9%) and epithelial keratitis (6.7%). Inflammation recurred in 65% of HSV patients, including stromal keratitis (24.9%), keratouveitis (18.6%), anterior uveitis (14.8%), and epithelial keratitis (6.3%). In both HZO and HSV, stromal keratitis and/or uveitis were the most common forms of recurrent disease: epithelial keratitis was least common. Of note, the suppressive antiviral regimen used was weaker (valacyclovir 500 mg daily or acyclovir 400 mg bid) than treatment planned for the current study (valacyclovir 1000 mg daily), suggesting that using a stronger regimen the effect may be even greater.

Remaining Gaps in Knowledge

The morbidity associated with chronic HZO is substantial and greater than HZ in other anatomic locations due to eye disease, longer duration of PHN, and greater risk of stroke. Thus, determining whether long-term antiviral therapy reduces the disease burden for patients and costs to society will fill a critical, substantial gap. Another significant gap in current clinical knowledge relates to effectiveness of early vs. delayed suppressive treatment. ZEDS will study patients with HZO of recent onset to determine if early suppressive antiviral treatment reduces chronic disease, and also patients with chronic disease to determine if delayed treatment is effective. Furthermore, ZEDS will evaluate the effects of age at disease onset, since this variable affects disease manifestations and may affect response to treatment. Patients with disease onset before age 60 more often have recurrent ocular inflammation, and patients with disease onset at age 60 and older more often have PHN and problems related to neurotrophic keratopathy (23). It is unknown if antiviral suppression benefits both age groups and whether the risk-benefit ratio varies by age at onset of disease. Therefore, the randomization to treatment group is stratified by these potentially important risk factors. Depending on the findings of the study, treatment recommendations might be tailored by age at disease onset, and/or by recent onset or chronic disease status.

Increased Incidence of HZ and HZO

Herpes zoster is caused by reactivation of VZV in people who have had chicken pox (varicella), the primary infection caused by VZV. There are about a million new cases of HZ in the US annually; up to 20% of these cases develop HZO, and 20-30% of these HZO patients develop chronic eye disease. Although the rate of HZ increases with age, the number of cases peaks in individuals age 50-59 (26). The incidence of HZ has been steadily increasing in the US among people age 40 and older for unknown reasons (27). The incidence of HZ in North America, Europe, and the Asia Pacific is increasing, and this trend started in the absence of varicella vaccination programs against chicken pox (28). HZ affects approximately 30% of the population, and HZO develops when HZ affects the first division of cranial nerve V (29).

ZEDS has the potential to have a major impact in improving outcomes and changing the standard of care of a common, serious chronic disease.

Disease Burden

HZ in general, and HZO in particular, can be associated with serious complications that result in diminished QOL, chronic eye disease, reduced vision, and even death (30). Most studies find that women are affected significantly more frequently than men with regard to HZ incidence, hospitalizations, and mortality (31-33). PHN persists for longer than 1 year in nearly half of patients older than age 70 (34-36). The direct medical cost burden of HZ may exceed a billion dollars annually in the US (35). In HZ patients who develop PHN, one-

year costs are more than 5 times greater than costs in HZ patients without PHN (34). The negative impact of HZ and PHN on health-related QOL is closely correlated with the severity of pain and persists as long as clinically significant pain (37, 38). A population-based study shows that HZ is a risk factor for developing major depression (39). Notably, PHN has been reported to be the most common cause of suicide in chronic pain patients over age 70 (40).

Publications that compare HZO with HZ occurring in other anatomic locations point to the risk of PHN and stroke being greater after HZO than HZ elsewhere (37, 41). PHN after HZO lasts longer and is more frequent than PHN after HZ in general, despite recommended acute antiviral treatment (36, 37, 41). Although potentially fatal strokes are an uncommon complication of HZ, HZO patients have a 4.5 times higher risk of stroke within a year after diagnosis compared to controls, and the adjusted hazard ratio of stroke after HZO is 4.3 compared to 1.3 after HZ (42, 43). In a self-controlled case-series population-based study, the risk of stroke for 6 months more than doubled after HZO compared to HZ in general (44). Although the risk of stroke after HZ is greatest in the short term, increased risk continues after the first year and is greatest in patients under age 40 (45).

Approximately 30% of HZO patients treated acutely with recommended oral antivirals have ocular complications at 6 months compared to 50% without this treatment (46, 47). Patients with ocular complications of HZO often have a chronic disease with manifestations that vary by age. Long-term topical corticosteroids are used to control ocular inflammation in most patients with chronic HZO disease. Use of oral antivirals is highly variable, with some academic cornea specialists prescribing them frequently and many ophthalmologists using them infrequently or not at all (24).

Support for Prolonged Antiviral Therapy in HZO-associated Ocular Disease

As documented above, the need for this large-scale trial is supported by extensive published evidence of chronic active VZV infection following HZ; and the recent observational study (above) reporting 50% rate of recurrent inflammation in HZO and 35% reduction of recurrent disease in patients on relatively low-dose suppressive antiviral treatment (1).

In addition, the landmark study of the long-term use of oral acyclovir for the prevention of recurrent herpes simplex virus (HSV) ocular disease, the Herpetic Eye Disease Study (HEDS) Acyclovir Prevention Trial (APT), demonstrated a 45% reduction in recurrent ocular disease over one year (4). It is therefore possible that in view of the similarities between HSV and HZO keratitis, suppressive antiviral treatment in HZO may reduce stromal keratitis and other anterior segment disease manifestations thought to be predominantly immune-mediated, as well as dendriform epithelial keratitis and iritis.

Taken together, these data make a convincing case that now is the right time to conduct this trial in order to obtain rigorous randomized controlled evidence to determine whether suppressing VZV infection reduces chronic anterior segment ocular disease and/or PHN in HZO.

2.2 RATIONALE

Valacyclovir is an FDA approved medication for the acute treatment of HZ, using a dose of 1000 mg three times a day for seven days, and for prolonged suppressive treatment of HSV genital disease in immunocompetent patients, using a dose of 1000 mg daily. This study evaluates the same dose as used for suppression of HSV genital disease for patients with HZO, a purpose that has not been approved by the FDA.

This proposal has been reviewed by the FDA and approved by the IRB at the NYU School of Medicine (NYUSoM).

This is the first prospective multicenter placebo-controlled RCT of prolonged suppressive antiviral treatment for chronic HZO or HZ in immunocompetent patients.

Assessment of Most Frequently Preferred Suppressive Antiviral Regimens for HZO by Cornea Specialists

The antiviral regimen to be studied was chosen in part on the basis of a second electronic survey conducted in preparation for this trial (25). Valacyclovir 500mg bid or 1000 mg daily was preferred by 64% (108/171). Valacyclovir is a prodrug of acyclovir, which has better oral absorption and bioavailability than acyclovir. The peak plasma concentration of acyclovir after 500 mg of oral valacyclovir is 3.28 mcg/mL and after 1000 mg of valacyclovir is 5.65 mcg/mL, according to the package insert. The median inhibitory concentration of acyclovir to reduce VZV plaque counts by 50% (IC50) is approximately 3 mcg/mL (48). The IC50 of acyclovir for VZV is higher than the IC50 of acyclovir for HSV type 1, which averages 0.45-1.47 mcg/mL (compared to the peak plasma concentration of 1.21 mcg/mL after 400 mg acyclovir, the dose that was effective in HEDS APT) (49). The VZV IC50 data supports the use of valacyclovir in this study. In order to facilitate compliance by having daily dosing rather than bid dosing, 1000 mg of valacyclovir will be used, the same dose approved for suppressive treatment of genital HSV disease in immunocompetent patients. Study participants will be randomized to take two 500 mg tablets of valacyclovir once daily or two tablets of placebo, because the 1000 mg valacyclovir tablet is too large to be encapsulated, as required for this masked placebo controlled study.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Risks to Study Participants Relative to Benefit to Study Participants and Others

The risk of suppressive antiviral treatment is low, and in view of the protocol measures to minimize them, the risk to study participants is low relative to the clinically important potential benefits in patients with HZO and HZ in general. If suppressive valacyclovir is effective, outcomes in HZO and PHN will be improved, benefiting afflicted study participants and society.

The blood test(s) is (are) associated with the risks and discomfort of any blood test requiring one tube, equivalent to two teaspoons of blood.

Risk of Study Drug Valacyclovir

The risk related to participation in this study relates to the risk of oral antiviral treatment with valacyclovir. Valacyclovir is approved and recommended for acute treatment of HZ, but not for chronic treatment of HZ. Previous studies of long-term suppressive treatment have been done in patients with HSV disease, using a similar dose of valacyclovir 1000 mg daily in immunocompetent patients (package insert). The most common side effects of suppressive treatment of recurrent genital HSV infections in immunocompetent adults with valacyclovir 1000 mg daily include headache (35%, compared to 34% with placebo), nausea (11%, compared to 8% with placebo), and abdominal pain (11%, compared to 6% with placebo), according to the package insert. Less common side effects include dysmenorrhea (8%, placebo 4%), depression (7%, placebo 5%), arthralgia (6%, placebo 4%), vomiting (3%, placebo 2%) and dizziness (4%, placebo1%). Rates of drug discontinuation in prior studies are not listed.

According to the package insert regarding laboratory results, hematologic abnormalities occurred in 0-0.7% in adults treated with valacyclovir 1 gram daily compared to 0.8-1.5% of adults treated with placebo. In addition, AST (SGOT) liver function test abnormalities occurred in 4.1% of adults on valacyclovir 1000 mg daily, compared to 3.0% on placebo. With regard to geriatric use, elderly patients age 65 and over are more likely to have renal or CNS adverse events and hematological and liver function problems are not mentioned. With regard to adults with liver impairment including cirrhosis, dosage modification is not recommended. Despite widespread use, there is little evidence that oral acyclovir (valacyclovir is prodrug of acyclovir) causes significant liver injury, or changes in serum liver enzyme levels (http:livertox.nih.gov/acyclovir.htm). Suppressive valacyclovir for HSV genital disease in immunocompetent patients at the same dose of 1000 mg daily and duration of one year, or longer, as used in our study has a long established safety profile with adverse events similar to placebo in numerous studies, both before and after its approval in 1995 (50). Long-term suppressive valacyclovir was not associated with laboratory abnormalities, including creatinine levels. Headache, nausea, and diarrhea were the most common adverse events attributed to the drug. Thrombotic microangiopathy that has been reported at high doses (8000 mg/d) for prolonged periods for prophylaxis of cytomegalovirus (CMV) infection, especially in severely immunosuppressed patients, has not been reported in 3050 participants in 4 trials of valacyclovir suppression of recurrent genital HSV.

If participants in this study develop side effects, such as gastrointestinal symptoms or headache, they will be instructed to take one tablet twice daily, as the study medication may be better tolerated in divided doses. Study participants with side effects that require discontinuation of the study medicine will continue to be followed, and be included in the study on an intention-to-treat basis. The study ophthalmologist will be allowed to restart the study medication after mild or moderate side effects resolve, if the study participant agrees. If side effects recur, the dose can be reduced to one pill daily, as this lower dose has been reported in a retrospective study to be effective in reducing recurrences in HZO (1).

Valacyclovir and Renal Insufficiency

Oral antiviral medications are generally very safe and can be used in patients with impaired renal function, but their dosage needs to be adjusted. For valacyclovir, a suppressive regimen of 1000 mg daily is reduced to 500 mg daily, in study participants with creatinine clearance < 30. Study participants on dialysis or with a baseline eGFR < 45 within one month prior to enrollment will be excluded from the study. On the basis of recommendations of a geriatrician, infectious disease specialist, and nephrologist, study participants with eGFRs 45 -59 will be eligible, based on assessment of potential risk/benefit ratio. Elderly patients are at increased risk for and most negatively impacted by HZO and often have reduced eGFR. Approximately 25% of people age 70 years and older can be estimated to have eGFRs between 45 and 59 (51). Study participants with a baseline eGFR of 45-59 will have repeat eGFRs prior to the three, six, nine, 12-month study visits. If the eGFR decreases to less than 45, the eGFR will be repeated. If on repeat testing the eGFR is less than 45 the study medication will be discontinued. Study participants will be told to see their primary care doctor and have eGFR repeated monthly until it is 45 or more. The study participant will continue to be followed, but the study medication will not be restarted.

The package insert contains a warning that acute renal failure can occur in the elderly, with or without reduced renal function. Nephrotoxicity is more frequent after intravenous than oral acyclovir. Serum creatinine >1.5 of the upper limit of normal occurred in 0.2% of HZ patients on 1000 mg oral valacyclovir tid and 0% of genital HSV patients on oral valacyclovir suppression with 1000 mg daily. Dehydration contributes to nephrotoxicity.

Study participants will be provided with a participant instruction sheet, which will include directions to maintain adequate hydration to decrease the likelihood of nephrotoxicity.

In a report of a population based study conducted in Canada with over 160,000 patients age 66 years or older, patients treated with the oral dose of acyclovir and valacyclovir used for acute HZ were compared to patients treated with famciclovir, with regard to the outcome of hospitalization within 30 days for acute kidney injury, and the risk was no higher with acyclovir and valacyclovir than famciclovir, a drug not known to be associated with renal toxicity (52). In this study, acute kidney injury occurred in less than 1% of patients (0.27% of acyclovir or valacyclovir treated patients and 0.28% of famciclovir treated patients). Risk factors for acute kidney injury included higher age (patients age 85 years or older: 0.62% in acyclovir/valacyclovir group and 0.71% in famciclovir group) and chronic kidney disease (1.46% in acyclovir/valacyclovir group and 1.86% in famciclovir group). Acute kidney injury related to acyclovir/valacyclovir is associated with birefringent needle crystals on urinalysis.

Although renal toxicity is an expected complication of valacyclovir, the frequency and severity of new or worsening renal disease will be monitored to determine if it is more common than expected. Study participants with follow-up eGFRs less than 45, or who develop urinary symptoms, will be referred to their primary care doctors for evaluation, including urinalysis to detect crystals, and management.

Valacyclovir and Pregnancy

Antivirals including valacyclovir (Category B) are used during pregnancy only if the potential benefit outweighs potential risk to the fetus. Women of reproductive age will need to agree to use a recommended form of contraception during the one year of study treatment, and pregnant women will be excluded by pregnancy blood testing within one month after a menstrual cycle prior to enrollment/randomization visit. Nursing women will be excluded. Study participants who become pregnant during the study will be withdrawn from the study medication and continue to be followed.

Valacyclovir and Central Nervous System (CNS) Reactions

The package insert contains a warning that agitation, hallucinations, confusion, encephalopathy, delirium and seizures can occur in patients taking valacyclovir, and that elderly patients are more likely to have these problems. HZO can also be complicated infrequently by central nervous system (CNS) vasculopathy (stroke). Study participants who have CNS adverse events will have their study medicine discontinued, at least temporarily, and be referred for neurological evaluation and treatment. If the treating physician thinks the safety of the study participant is an issue, the 24/7 help line is available, and, if necessary, to differentiate between drug and disease related CNS disease, the medical monitor can initiate the process to unmask study medication (see Manual of Procedures, MOP). CNS complications of HZ are thought to be rare, but may be under-diagnosed, and additional information regarding their frequency may be obtained in the placebo treatment arm of the study.

Valacyclovir and Thrombotic Thrombocytopenic Purpura /Hemolytic Uremic Syndrome (TTP/HUS)

The package insert has a warning that TTP/HUS has occurred in patients with advanced HIV disease and bone marrow or renal transplant recipients on 8 grams per day of valacyclovir, a dose used for cytomegalovirus, not herpes zoster or simplex. Since immunocompromise is an exclusion criterion and the dose of valacyclovir is much lower, 1 gram per day, TTP/HUS will be considered an unanticipated and serious adverse event in this study.

Protections Against Risk

The investigational plan is specifically designed to manage and minimize risks through careful selection of study participants and suppressive antiviral treatment regimen, thorough training of study investigators and coordinators, adherence to the pre-determined time points to assess study participant clinical status, and regular clinical monitoring by study Coordinating Center (CC) personnel and the Data and Safety Monitoring Committee (DSMC). Suppressive treatment with valacyclovir 1000 mg daily of immunocompetent individuals age 18 years and older is FDA approved and recommended for herpes simplex virus (HSV) genital disease. This study evaluates the efficacy and safety of valacyclovir, at the same dose used for HSV suppression, for study participants with a different diagnosis, HZO, for which valacyclovir is approved at a higher dose, for a short duration. HZO patients are generally older than HSV patients, with approximately mean age of onset of HZO of 52 years compared to ocular HSV with a mean age onset of 37 years (2, 4, 53).

In order to minimize risks of valacyclovir in an older population of study participants, a baseline eGFR will be obtained prior to enrollment. If the eGFR is 60 or more, i.e. normal, it will not be repeated for study purposes. In order not to unfairly exclude many elderly study participants by requiring an eGFR of 60 or more, a baseline eGFR of 45 or more is an eligibility criterion. Study participants with eGFRs between 45-59 will have repeat eGFR testing every 3 months during treatment with the study drug. If the eGFR decreases to less than 45, the eGFR will be repeated. If repeat eGFR is 45 or more, the study medication will be continued, and the eGFR will be repeated prior to the next study visit. If on repeat testing the eGFR is less than 45 the study medication will be discontinued. Study participants will be told to see their primary care doctor and have eGFR test repeated monthly until it is 45 or more. The study medication will not be restarted, and the participant will continue to be followed for safety assessments.

There are no known study-related risks in addition to the use of the study medication, oral valacyclovir and blood testing.

2.3.2 KNOWN POTENTIAL BENEFITS

It is unknown whether prolonged suppressive antiviral treatment with valacyclovir reduces complications of HZO, including ocular disease and PHN, although oral antiviral medication is prescribed by approximately 30% of corneal specialists according to one study, and reported effective in significantly reducing episodes of recurrent HZO disease in another recent observational study (1, 24). If this study determines that valacyclovir is effective and safe in reducing complications of HZO, study participants randomized to receive valacyclovir may directly benefit, as well as future HZO patients treated using this evidence. If the study treatment is effective and safe in decreasing the severity, duration and frequency of PHN after HZO, this may be generalizable to HZ in other locations, and benefit many patients with PHN. If suppressive antiviral treatment is ineffective or study participants receive placebo treatment, participants will not directly benefit from participation in this research. If treatment is ineffective, its current ad hoc usage in the absence of evidence will be reduced.

3 OBJECTIVES AND PURPOSE

The objective of this double-masked, multicenter placebo controlled RCT is to evaluate whether or not prolonged suppressive oral antiviral treatment with valacyclovir 1000 mg/daily reduces complications of HZO, in immunocompetent study participants, compared to treatment with placebo and standard care without prolonged systemic antiviral treatment, thereby improving the outcomes in this common and potentially vision

and life-threatening disease. Valacyclovir, a prodrug of acyclovir, has been chosen as the antiviral agent to be used in the trial due to its superior bioavailability.

Central Hypothesis:
Prolonged suppressive oral antiviral treatment with valacyclovir 1000 mg daily, compared to placebo, will be effective in reducing complications and in improving clinical outcomes in HZO.

Primary Objective:
The primary objective is to test the hypothesis that long-term suppressive antiviral therapy can reduce complications of HZO by conducting a double-masked, placebo-controlled RCT of oral valacyclovir 1000 mg daily. Specifically, we will evaluate whether or not long term suppressive antiviral therapy compared with placebo therapy delays the time to the first occurrence of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis (accompanied by prespecified changes in treatment; see MOP) by 12 months (primary endpoint) in immunocompetent study participants with HZO who have a history of one of these disease manifestations within the year prior to enrollment. The primary endpoint is measured by the time to first occurrence of any one of these specified complications associated with pre-specified treatment – see MOP.

Secondary Objectives:
The secondary objectives are:

- to evaluate the effect of treatment on the primary endpoint at 18 months (6 months after the completion of study drug treatment)
  - by comparing the rates of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis in study participants randomized to valacyclovir versus placebo
  - by comparing time to development of the primary endpoint over the 18-month period from randomization and
  - by comparing the occurrence of the primary endpoint during the 6-month post treatment period.
- to test the hypothesis that suppressive treatment for 12 months with oral valacyclovir 1000 mg daily reduces the incidence, severity and duration of post herpetic neuralgia (PHN) compared to placebo at 12 and 18 months in study participants with HZO.
- to test the hypotheses that vaccination against herpes zoster with the Recombinant Zoster Vaccine (RZV) may impact the natural history of HZO, and that suppressive antiviral treatment with valacyclovir 1000 mg daily compared to placebo may alter the impact of this vaccination on HZO activity during 12 months of study treatment.

See sections 4.2.2 for details regarding additional objectives.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

The study is a double-masked, multi-center RCT that will enroll immunocompetent study participants age 18 years and older who have HZO diagnosed at variable times in the past, with an episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis within one year of enrollment. Eligible study participants will be randomized in a 1:1 ratio to long-term suppressive treatment with oral valacyclovir 1000 mg

daily or placebo for one year, and followed every 3 months for a total of 18 months, to determine outcomes of new or worsening anterior segment ocular disease (e.g. dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis) and/or severity and duration of postherpetic neuralgia during 12 months of treatment and for 6 months following treatment discontinuation. Within each center, participants will be randomized within four strata, defined by age at ***onset*** of HZO (less than 60 years or 60 years and greater) and by recent onset or chronic HZO (recent onset defined as HZO diagnosed within 6 months of ***enrollment/ randomization***, or chronic defined as HZO diagnosed 6 months or more prior to enrollment/randomization).

4.2.1 PRIMARY ENDPOINT

The primary endpoint is the time to first occurrence of new or worsening episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, requiring pre-specified changes in treatment (see MOP) during the twelve months of treatment. The primary endpoint is compared for participants randomized to study medication or placebo.

To assess the primary objectives, study participants will be monitored at each visit for new or worsening of any of the following conditions

1. Dendriform epithelial keratitis
2. Stromal keratitis
   a. Without ulceration
   b. With ulceration
3. Endothelial keratitis
4. Iritis

The endpoint of first occurrence of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis will be determined by clinical examination requiring pre-specified changes in treatment for the same disease manifestation (see MOP for definition), as there are no validated confirmatory biomarkers or other tests. Primary endpoints will be reviewed by Clinical Event Review Committee (CERC). See MOP.

4.2.2 SECONDARY ENDPOINTS

To assess the secondary objectives, the study participants will be monitored at each visit for the following events:

1. Time to development and number of episodes of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, requiring pre-specified changes in treatment (see MOP), during the 18 months following randomization, that includes the 6 months following cessation of treatment; and during the 6 months following the end of the 12 month treatment period.
2. The incidence, severity, and duration of PHN at one year of treatment, and after the 6-month post-treatment follow up.
3. Impact of Recombinant Zoster Vaccine (RZV) vaccination on primary endpoints during 12 months of study treatment.

4. Development of specific manifestations of HZO, classified as dendriform epithelial keratitis, stromal keratitis (all types), endothelial keratitis, iritis requiring pre-specified changes in treatment (see MOP), neurotrophic keratopathy with or without melting and/or microbial superinfection, episcleritis, and/or scleritis during the twelve months of treatment.
5. Secondary glaucoma determined by IOP and treatment required.

4.2.3 EXPLORATORY ENDPOINTS

1. Changes in strength and/or frequency of prescribed topical corticosteroids at 12 and 18 months.
2. Occurrence of stroke
3. Occurrence of temporal arteritis/giant cell arteritis
4. Occurrence of myocardial infarction
5. Occurrence of new or worsening malignancy
   a. Solid tumor (other than non-melanoma skin cancer)
   b. Hematologic malignancy
   c. Lymphoma
6. Time to development and number of episodes of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, with a recent substantial reduction in treatment during 12 months of treatment.
7. Impact of suppressive antiviral treatment prior to enrollment on study outcomes.

Rates of these events will be estimated among study participants randomized to valacyclovir and placebo.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

To be eligible for study participation, an individual must meet all of the following criteria:

1. Ability to understand, and willingness and ability to read and sign, the informed consent form.
2. Ability to understand and follow instructions and study procedures.
3. Willingness to comply with all study procedures and be available for the duration of the study.
4. Ability to take oral medication, and are willing to adhere to study medication regimen.
5. Age 18 years or older.
6. Diagnosed with HZO in one eye based on both of these criteria:
   a. History of characteristic unilateral, usually vesicular, HZO rash in the dermatomal distribution of cranial nerve V1 or V2.
   b. Medical record documentation of an episode of active dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO within the preceding year. This episode of active anterior segment ocular disease may be due to HZO of recent onset (within the preceding 6 months); or chronic HZO (with onset six or more months ago); may be new, worsening, or recurrent disease after a period of inactivity; and may occur after medication was reduced.
      i. Study participants with chronic HZO must be on a stable treatment regimen and off antivirals for at least 30 days before enrollment. Study participants with chronic HZO who do not meet this criterion may be rescreened, if they are able to meet this criterion within 3 months after the study visit.

This is not a requirement for study participants with recent onset HZO, who may be enrolled at any time, preferably after completing recommended acute antiviral treatment, if prescribed, is completed. <u>They can be on variable dose of steroids, and only need to be off oral and topical antivirals by the enrollment visit.</u>

7. For females with reproductive potential, willingness to use highly effective contraception (e.g., hormonal contraception, barrier contraception, intrauterine device, or abstinence).

5.2 PARTICIPANT EXCLUSION CRITERIA

<u>An individual who meets any of the following criteria will be excluded from participation in this study:</u>

1. History of immunocompromised status as defined by current CDC contraindications for the vaccine against zoster (44).
   a. Study participants who are diagnosed with leukemia, lymphomas or other malignant neoplasms affecting bone marrow or lymphatic system, unless leukemia in remission and off chemotherapy for at least 3 months.
   b. Study participants who are diagnosed with Acquired Immune Deficiency Syndrome (AIDS) or presents with other clinical manifestations of Human Immunodeficiency virus (HIV) including CD4 count of ≤ 200 cells/ml.
   c. Study participants on immunosuppressive therapy including:
      i. High-dose corticosteroids (greater than equivalent of prednisone 20 mg/day within 1 month)
      ii. Chemotherapy, other than low dose used for treatment of immune-mediated diseases within 3 months
      iii. Study participants receiving recombinant human immune mediators and immune modulators, especially antitumor necrosis agents, within 1 month prior to enrollment
   d. Study participants with unspecified cellular immunodeficiency.
   e. Study participants with history of hematopoietic stem cell transplantation.
2. Medical history of a systemic disease and thought likely to meet one of the exclusion criteria listed in exclusion criterion #1 during the 18-month study period.
3. Renal insufficiency:
   a. Requires dialysis or has history of renal transplant or
   b. eGFR less than 45, determined within 3 months preceding enrollment.
4. Allergy or adverse reaction to valacyclovir or acyclovir.
5. History of vaccination against zoster within one month prior to enrollment. Study participants who meet this exclusion criterion may be screened and enrollment delayed until eligible within 3 months. If the study participant receives the Herpes Zoster Subunit vaccine (Recombinant Zoster Vaccine (RZV), Shingrix), rescreening should take place one month after the second required dose of the vaccine.
6. Keratorefractive surgery, other than limbal relaxing incisions or astigmatic keratotomies at the time of cataract surgery, within 5 years of enrollment, or keratoplasty of the involved eye with zoster.
7. On systemic antivirals with activity against herpes within the past 30 days, including acyclovir, valacyclovir, or famciclovir, for any reason except for treatment of recent onset HZO, including investigational drug trial.
8. History of another condition that may require treatment with one of these three antivirals listed above in exclusion criterion #7, during the course of the study; study participants who require chronic suppressive antiviral treatment with these medications will be excluded.

9. Sexually active women who are pregnant, nursing, or in their reproductive years who do not agree to use contraception during the 1-year treatment period.
10. Incarceration
11. Any condition or circumstance that in the opinion of the study investigator, would place the study participant in increased risk or affect his/her full compliance or completion of the study.
12. Participation in a clinical study testing a drug, biologic, device or other intervention within the last 30 days from enrollment visit. Study participants who meet this criterion may be rescreened.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The study protocol, informed consent form, recruitment materials and all participant materials will be submitted to the responsible Institutional Review Board (IRB) registered with the US Office for Human Research Protections (OHRP) under a Federal Wide Assurance (FWA) for review and approval.

Eligible study participants will be identified by study investigators and coordinators at Participating Clinical Centers (PCC) by retrospective (e.g. computerized search of HZO diagnostic codes) and prospective methods (e.g. advertising, referrals from other doctors). All recruitment methods, advertising and materials will be submitted to responsible IRBs prior to release. Potential study participants may be contacted through IRB approved communication methods. Pre-screening interview questionnaires and screening logs to assess patient eligibility and interest, together with materials to be used for collection of patient information prior to the consenting process will be submitted to responsible IRBs for review and approval. (See MOP for recruitment and retention strategies.)

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Study participants may voluntarily withdraw from study participation at any time upon request.

Study participants will be followed for a minimum of 12 months and through the final visit, approximately 18 months after enrollment, whether or not they have reached the primary endpoint of time to the development of the first occurrence of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis, or discontinue the study medication. Every effort will be made to collect this follow up information. Study participants who withdraw without an event will be considered censored in the analyses.

A study participant may be withdrawn, if, the study investigator determines that an event or medical condition has occurred that would make continued study participation not in the best interest of the study participant.

Efforts will be made to refer study participants to another PCC if they move or are away at the time of study visits. All efforts should be made to locate or communicate with study participants who have missed study visits. (e.g. contact by telephone, written communication, text, email, through participant's family, friends or healthcare proxy which were provided by study participants to PCC, to determine if outcome events have occurred.)

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study chair, funding agency, the IND sponsor and the FDA. If the study is prematurely terminated or suspended, the study chair will promptly inform the IRB and the PCC principal investigators, and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The CC at NYULMC will purchase 500 mg pills of lactose-free generic valacyclovir and have them sent to a drug manufacturer for over encapsulation. An over encapsulated matching pill will be backfilled with similar excipients contained in the active agent to create the matching placebo pill. Both active and placebo pills will be sent to a Drug Distribution Center (DDC). The DDC will receive, store, and dispense study medication to PCCs. Upon receipt of the of the study treatment supplies in individually labeled bottles at the PCC, drug handling and accountability procedures must be followed (see MOP). At the time of randomization, the appropriate drug supply will be dispensed to study participants. The study medication is dispensed only after eligibility is confirmed and study participant age at onset of HZO and duration of HZO at time of enrollment/ randomization is provided to the Electronic Data Capture web-based interactive computer system. At the 3, 6, 9, and 12-month follow-up visit, unused pills will be counted by the coordinator at the PCC. Unused drug will be returned to the ZEDS CC for disposal; PCCs can dispose of the unused drug on site if they have a policy compliant with applicable regulations.

There will be reconciliation of drug shipped, drug consumed, and drug remaining at each PCC as specified in the MOP.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Valacyclovir was approved for the treatment of HSV and HZ in 1995, and has been available as a generic drug since 2009. (See MOP and MOP appendix: FDA package label for drug information). Generic study drug will be purchased from a manufacturer.

The drug manufacturer will deliver the study drugs to a DDC. The DDC will label and distribute the study medication to the PCCs as directed by the CC at NYUSoM. The DDC will repackage the masked study medication (active or placebo) into bottles with child-resistant caps and tamper-foil seals.

Study participants will be given a sufficient supply of encapsulated study medication in labeled bottles at the enrollment, 3, 6, and 9-month follow-up visits. Each bottle of study medication will be labeled to ensure masking and provision of study medication in accordance with randomization assignment. The study label will also state the expiration date. (See MOP)

6.1.3 PRODUCT STORAGE AND STABILITY

The study medication is to be stored at room temperature 15° to 25°C (59° to 77°F) in a secure location (e.g. locked cabinet, restricted access pharmacy) accessible only to designated staff at the PCC (see MOP for drug storage, drug stability, expiration time, or instructions for when bottle seal is broken).

6.1.4 PREPARATION

No further preparation of the study medication is required by study staff or study participant.

6.1.5 DOSING AND ADMINISTRATION

Eligible study participants will be randomized in a 1:1 ratio to suppressive treatment with oral valacyclovir 1000 mg daily or placebo for one year. Study participants will be followed every 3 months for a total of 18 months, 6 months following completion of the 12-month treatment period. Study participants will be instructed to take 2 pills once daily.

6.1.6 ROUTE OF ADMINISTRATION

Study medication will be taken by study participants orally.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

The starting dose of valacyclovir is 1000mg daily. There is no dose escalation.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Study investigators will be trained and study participants will be instructed regarding dose adjustments of study medication.

Use of Divided Dose of Study Medication for Intolerance

If the study participant has mild to moderate side effects to the study medication, the medication may be temporarily discontinued. The study participant may take one pill twice daily, instead of two pills once daily, as it may be better tolerated.

Use of Reduced Dose of Study Medication for Intolerance

If the study participant has mild to moderate side effects to the study medicine when taken in divided doses, the medication may be temporarily discontinued. The study participant may take a reduced dose of one capsule daily.

Discontinuation of Study Medication due to Intolerance

If intolerance to the study medication is moderate or worse after restarting the study medication in divided doses and reducing the dose, the study medication will be permanently discontinued. The study participant will be treated at the discretion of ophthalmologists involved in their care, and continue to be followed. Open label use of other antivirals after study medication is discontinued will be collected and monitored.

Discontinuation of Study Medication

If the study participant develops a contraindication to valacyclovir during the course of the study (See 5.2.).The study medication will be permanently discontinued and the study participant will continue to be followed.

Discontinuation due to Pregnancy

If a study participant becomes pregnant, the study medication will be discontinued and the study participant will continue to be followed. If a study participant thinks she may be pregnant, a pregnancy test will be performed.

Discontinuation due to Worsening Chronic Kidney Disease

If a study participant develops worsening chronic kidney disease with confirmed eGFR less than 45, the study medication will be discontinued and the study participant will continue to be followed.

Discontinuation due to Acute Kidney Failure

If a study participant develops acute kidney failure, and requires temporary or permanent dialysis, the study medication will be discontinued and the study participant will continue to be followed.

Temporary Discontinuation due to Vaccination Against Zoster

If the study participant decides to get the Zoster Vaccine Live (ZVL),Zostavax, manufactured by Merck) against zoster, the study medication will be discontinued one day before and resumed one month after vaccination. If the study participant gets the Recombinant Zoster Vaccine (RZV), also referred to as the herpes zoster subunit vaccine (Shingrix manufactured by Glaxo Smith Kline), the study medication is to be continued. As of January, 2018 the CDC recommends the RZV as preferred over ZVL.

Temporary or Permanent Discontinuation due to Use of Open Label Oral Valacyclovir, Acyclovir or Famciclovir Treatment for Other Conditions

- If the study participant develops ocular, orofacial, or genital HSV disease and requires a short term (maximum two weeks) course of oral antiviral treatment, the study medication will be temporarily discontinued during this treatment, and resumed afterwards. If the study participant requires long-term antiviral treatment for HSV, the study medication will be permanently discontinued, the participant will continue to be followed in the study, and the study medication will not be unmasked.
- If study participant develops HZ in another anatomical location, study medication will be discontinued, the participant will be given recommended acute antiviral treatment for 7 days, and then the study medication will be resumed.
- If study participant is diagnosed with central nervous system disease (including stroke) due to zoster, study medication will be discontinued while participant receives intravenous antiviral treatment, sometimes followed by a course of oral antiviral treatment, and resumed afterwards, if the treating neurologist agrees. The study participant will continue to be followed in the study.
- If study participant develops any other medical condition that necessitates treatment with valacyclovir, acyclovir, or famciclovir, the study medication will be discontinued while on open label treatment and resumed afterwards,. The open label treatment period should not usually exceed two weeks.

Temporary Discontinuation due to Short-term (maximum two weeks) Open Label Use of Valacyclovir, Acyclovir or Famciclovir for HZO

If the study participant develops a possible primary endpoint - new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis - and the study investigator thinks the study participant may benefit from a one to two-week course of open label oral antiviral treatment, the study medication will be temporarily discontinued, and resumed when the course of open label treatment is completed. (After a study participant develops a possible primary endpoint, if topical antiviral treatment is prescribed, the study medication is continued.)

Permanent Discontinuation due to Prolonged Open Label Use of Valacyclovir, Acyclovir or Famciclovir for HZO

If the study participant develops a possible primary endpoint - new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis - and the study investigator thinks the participant may benefit from prolonged open label antiviral treatment, the study medication will be discontinued, and the participant will continue to be followed. Any open label use of antivirals will be collected and centrally monitored.

6.1.9 DURATION OF THERAPY

The duration of therapy is one year (12 months) from study enrollment/randomization. All study participants randomized will be included in the analyses of the primary efficacy endpoint in this intent to treat trial.

6.1.10 TRACKING OF DOSE

At the 3, 6, 9, and 12-month follow-up study visits, study participants will return the study medication bottles with all unused study medicine and completed diary cards. Unused pills will be counted by PCC study staff to determine compliance. Diary cards will be provided to study participants to enhance compliance (see MOP). The importance of compliance will be included on the participant instruction sheet and will be discussed at each study visit during the one year of treatment by the study investigator and coordinator (see MOP).

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Study medication will be sent to the PCCs by the DCC in masked labeled bottles. Designated study staff at the PCCs will distribute the medication to participants at Visits 2, 3, 4, and 5, and will be required to complete relevant drug accountability documents (see MOP). Study participants will be asked to return the medication bottles and any unused medication at study visits 3, 4, 5 and 6.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

The following procedures will be performed for study-specific purposes:

- Review of inclusion/exclusion criteria for eligibility
- Informed consent
- Collection of demographic information
- eGFR and Pregnancy Tests
- Collection of HZO treatment information
- Randomization: Eligible participants will be randomized to receive either valacyclovir or matching placebo.
- Study specific history: assessment of post herpetic neuralgia using question #3 of Zoster Brief Pain Inventory (ZBPI)
- Study specific ophthalmic exam of the eye with HZO
- Completion of medical event form
- Collection of information regarding any serious adverse events (SAEs)
- Assessment of study adherence: counts of returned unused pills and study participants diary card records.
- Monthly contact between study visits, eg. telephone, email, text, or letter is encouraged. (See MOP)

7.1.2 STANDARD OF CARE STUDY PROCEDURES

The following procedures will be performed as standard of care:

- History and exam of zoster eye unrelated to zoster
- History and exam of the non-zoster eye
- History and exam at visits other than required study visits

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

The following laboratory procedures/evaluations will be performed at the study participant's closest study designated diagnostics laboratory, or local laboratory when necessary:

- Blood test for eGFR prior to enrollment: All study participants will be asked to obtain a serum creatinine blood test for eGFR determination. Measurement of creatinine to calculate eGFR will not be required if it has been completed in the past 30 days and the results are available for investigator review. Subjects with an eGFR of 45-59 will be enrolled in the study, but asked to have repeat testing at intervals throughout the study, as described in section 7.3. This is a study-specific procedure and is not standard of care.
- Blood test for pregnancy prior to enrollment: Women of childbearing potential will be asked to take a pregnancy test. During the study, women who are able to become pregnant must agree to use a medically accepted method of birth control, including hormonal methods, barrier method, intrauterine device, or abstinence, while on the study drug. This is a study-specific procedure and is not standard of care.
- Urinalysis: For study participants with acute kidney disease to look for crystals associated with valacyclovir.
- A urine dipstick test for pregnancy will be conducted by PCC study staff if a study participant suspects pregnancy at the time of a study visit.

7.2.2 OTHER ASSAYS OR PROCEDURES

Not applicable.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Not applicable.

7.2.4 SPECIMEN SHIPMENT

Not applicable.

7.3 STUDY SCHEDULE

7.3.1 SCREENING/CONSENT

HZO patients who are thought likely to be eligible for the study on the basis of an eligibility checklist and review of their medical records by the study investigator and/or coordinator will have a screening visit. The following will be performed/obtained:

- The consent form will be reviewed and signed.

- Study specific review of medical records.
- Study specific review of demographics.
- Review of study inclusion/exclusion criteria.
- Blood test for eGFR ordered.
- Blood test for pregnancy order for women of child bearing potential

Measurement of creatinine to calculate eGFR will be ordered within 30 days of enrollment, unless it has already been obtained within this time period. If the eGFR is 45 or more, the study participant is eligible for enrollment. If the eGFR is 45-59, it will be repeated within 30 days of the 3, 6, 9, and 12 month study visits.

If a woman of child-bearing potential who has provided written informed consent is found to be eligible and is interested in participating in the study, a pregnancy test will be ordered A negative pregnancy test is required within 30 days, preferably within 2-3 days of enrollment and after a menstrual cycle.

The eGFR and pregnancy tests are study-related procedures and not part of routine care. During the study, women who are able to become pregnant must agree to use a medically accepted method of birth control, including hormonal methods, barrier method, intrauterine device, or abstinence, while on the study drug.

7.3.2 ENROLLMENT/RANDOMIZATION

At the enrollment/randomization visit, the following will be performed/obtained:

- Study specific history of HZO treatment.
- Study specific ophthalmic exam, including: routine visual acuity and manifest refraction, (not standardized or by certified technician) anterior segment ophthalmic exam, measurement of corneal thickness, dilated fundus exam and pachymetry of study eye.
- Study specific review of inclusion/exclusion criteria.
- Study specific post herpetic neuralgia score and review of medication history for PHN.
- Randomization: Study participants who have provided written consent and meet study entry criteria will be randomized within center to one of the four strata depending on their age at the *onset* of HZO (age less than 60 years compared to 60 or older) and duration of HZO at the time of *enrollment and randomization* (less than 6 months compared to greater than or equal to 6 months).
- Study participants will be dispensed an adequate supply of study medication consistent with randomization assignment and will receive instructions to take 2 pills once daily, in addition to any other medication(s) (See MOP).
- Study participants will receive instructions to maintain adequate hydration to decrease the likelihood of nephrotoxicity (See MOP).
- Study participants will a diary to record when study medication is taken.
- If the baseline eGFR was 45-59, the study participant will be given a prescription for repeat testing prior to their next visit.
- An appointment to return during a specified window of days for their three-month follow-up visit will be scheduled.

The importance of compliance with the study medication and visits will be emphasized. Study participant's contact information will also be confirmed at each study visit (see MOP).

7.3.3 FOLLOW-UP STUDY VISITS

Study visit number at 3, 4, 5 occurring at months 3, 6, and 9 after enrollment:
At the follow-up visits, the following activities will occur/be performed:

- Study specific history of HZO treatment.
- Study specific anterior segment ophthalmic exam.
- Assessment of post herpetic neuralgia score and review of medications taken for PHN.
- Returned study medication pills will be counted to assess medication compliance. Diaries will be returned.
- Assessment for possible medical events of interest
- Assessment for possible primary endpoints.
- Assessment for possible SAEs.
- Study participants will be dispensed an adequate supply of study medication and will receive instructions to take 2 pills once daily. in addition to any other medication(s). At the discretion of the investigator, dosage may be adjusted to one pill twice daily or once daily and appropriate study participant instruction sheet will be provided (see MOP).
- Study participants will receive a diary to record when study medication is taken.
- If the study participant had a baseline eGFR of 45-59 repeat eGFRs will be completed prior to the 3, 6, 9 month study visits.
  - If eGFR is 45 or above, study medication will be continued.
  - If eGFR is less than 45, the study medication will be discontinued, and the eGFR will be repeated within one week. If on repeat testing the eGFR:
    - is 45 or more, the study medication will be resumed, and eGFR will be repeated within 30 days of the next study visit.
    - is less than 45, study participant will be given a prescription to visit their local study designated laboratory for monthly eGFR testing until it is 45 or more. In addition, study participants will be told to see their primary care doctor for management of their kidney disease. The study medication will not be resumed, and the study participant will continue to be followed in the study.
- An appointment to return during a specified window of days for their three-month follow-up visit will be scheduled.
- The study participant will be instructed to continue their non-study treatment.

The importance of compliance with the study medication and visits, will be emphasized at each study visit. Study participant's contact information will also be confirmed at each study visit (see MOP).

Visit 6 (12 month follow-up visit):

At this visit, study medication will be discontinued. The visit will be the same as the 3, 6, and 9- month follow-up visits, with the addition of:

- Study specific ophthalmic exam including direct fundus exam. If visual acuity is 2 or more lines lower than enrollment visual acuity, then a routine refraction will be done in the study eye. If visual acuity is not improved by a routine refraction, then a dilated fundus will be performed.

- In study participants with enrollment eGFR 45-59, an eGFR test will be done prior to this visit:
- if 45 or above, will not be repeated (this is not part of routine care).
- If less than 45, eGFR will be repeated within one week. If on repeat testing the eGFR:
  - is 45 or more, it will not be repeated.
  - is less than 45, study participants will be given a prescription to visit their local study designated laboratory for monthly eGFR testing until it is 45 or more. In addition study participants will be told to see their primary care doctor for management of their kidney disease, and the study participant will continue to be followed.
- The study participant will be instructed to continue their non-study treatment.

Visit 7 (15 month follow-up visit):

The visit will be the same as the 3, 6, and 9- month follow-up visits (please note there is no study medication involved and eGFR testing is not repeated (see MOP).

7.3.4 FINAL STUDY VISIT

Visit 8 (18 month final study visit)

The visit is the same as the 15 month follow-up visit (Visit 7). This visit is the last study visit for the participant and the study completion form will be filled out (see MOP).

7.3.5 EARLY TERMINATION VISIT

This visit is similar to the 18-month visit (See MOP).

7.3.6 NON-STUDY VISIT (UNSCHEDULED/SCHEDULED VISIT)

At non-study visits, a standard office medical exam will be completed (routine care) (See MOP). A CRF for non-study visit will be completed by the study staff. Additional CRFs may be required if a primary endpoint may have occurred at the time of the non-study visit.

7.3.7 SCHEDULE OF EVENTS TABLE

Source documents include medical records, images and all other information necessary to reconstruct and evaluate the clinical trial. Study monitors will compare data entered in electronic CRF's to information in source documents to verify the accuracy of trial data.

Please see Table 1 for Schedule of Events.

Table 1: Schedule of Events.

Procedures	Screening/consent (Visit 1)	Enrollment/Randomization (Visit 2)	3-month Follow-up (Visit 3)	6-month Follow-up (Visit 4)	9-month Follow-up (Visit 5)	12-month Follow-up (Visit 6)	15-month Follow-up (Visit 7)	18-month Follow-up (Visit 8)
Informed consent	X							
Study specific review of medical records[1]	X	X						
Study specific review of demographics	X							
Review of inclusion/exclusion criteria[2]	X	X						
Order pregnancy test[3]	X							
Order serum creatinine blood test for eGFR determination[4]	X[4,5]							
Repeat eGFR prior to visit only *if baseline eGFR = 45-59*[5]			x	x	x	x		
Study specific history of HZO treatment		X	X	X	X	X	X	X
Study specific ophthalmic exam		X[6]	X[7]	X[7]	X[7]	X[8]	X[7]	X[7]
PHN score and review of medication history for PHN		X	X	X	X	X	X	X
Randomization		X						
Medication dispensed and instruction sheet provided		X	X	X	X			
Assessment of possible medical events			X	X	X	X	X	X
Assessment of possible primary endpoints			X	X	X	X	X	X
Assessment of possible SAEs			X	X	X	X	X	X

[1] Study specific review of the participant's medical history is reviewed at the screening visit and the case report form is completed at the enrollment visit. If the study participant is ineligible, the form is not completed.
[2] Inclusion/exclusion criteria are reviewed at the screening visit and the case report form is completed during the enrollment visit. If the study participant is ineligible at the screening visit, the form is completed then.
[3] A serum pregnancy test is required of women of child-bearing potential, who have provided written informed consent and are found to be eligible. The pregnancy test should preferably be done 2-3 days after a menstrual cycle. A urine dipstick test for pregnancy will be conducted by study staff if a study participant suspects pregnancy at the time of a study visit.
[4] A serum creatinine blood test for eGFR determination will not be required if one has been completed in the past 30 days and the results are available for review.
[5] Study participants with an eGFR of 45-59 will be enrolled in the study, but asked to have repeat testing at intervals throughout the study.
[6] At enrollment/randomization, the study specific ophthalmic exam of the study eye consists of routine manifest refraction, anterior segment ophthalmic exam, dilated fundus exam and pachymetry.
[7] At visits 3, 4, 5, 7 and 8, the study specific ophthalmic exam consists of an anterior segment ophthalmic exam.
[8] At visit 6, the study specific ophthalmic exam of the study eye consists of a direct fundus exam. If visual acuity is 2 or more lines lower than enrollment visual acuity, then a routine refraction will be done in the study eye. If visual acuity is not improved by a refraction, then a dilated fundus will be performed.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

The FDA-approved label for the use of valacyclovir does not list contra-indications to the use of other medications concomitantly with valacyclovir.

While it is recommended that study participants with HZO receive acute high dose antiviral treatment within 72 hours of the onset of the rash for seven days, and study participants will be asked their history regarding this, it will not be required for entry into the study, as it would make many participants ineligible. Optimal medical treatment aside from acute antiviral treatment has not been determined for HZO. The study medication will be given to study participants in addition to standard treatment. It is the purpose of this study to evaluate the efficacy of prolonged suppressive antiviral treatment, to determine whether it should become optimal medical therapy in the future. Aside from the antiviral medications valacyclovir, acyclovir, and famciclovir, all other concomitant systemic medications are allowed during the study. Study participants who require topical steroids will be strongly recommended to be treated with prednisolone acetate 1% or loteprednol 0.5% at the discretion of their study investigator. Study participants who develop dendriform epithelial keratitis will be recommended to be treated with topical ganciclovir (0.15%) five times daily until healed and then two times daily for two weeks. These topical steroids and antiviral medications are standard care.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Until a possible primary outcome is reached open label treatment of HZO eye disease with oral valacyclovir, acyclovir, or famciclovir is prohibited for duration of the study (i.e. 18 months).

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Following completion of the 18-month study the study participant will return to the care of their ophthalmologist and treated at their physician’s discretion.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

It is the responsibility of the PCC Principal Investigator (PI) to oversee the safety of the study at his/her center. This safety monitoring will include training, careful assessment and appropriate reporting of serious adverse events (see MOP).

The CC monitoring of serious adverse events will be reviewed by masked medical monitors. These medical monitors will also have the ability to unmask treatment if required in an emergency for study participant safety (see MOP).

At each contact with the study participant, the PCC study investigator or designated study team member will assess for possible medical events of interest, possible primary endpoints and for possible SAEs (see MOP).

8.1.1 COLLECTION OF SELECTED ADVERSE EVENTS (AE)

Adverse events that result in temporary or permanent discontinuation of study medication will be required to be reported by the PCC to the CC as appropriate.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious, unexpected adverse events related to the study treatment will be primary safety endpoints. A serious adverse event is any untoward occurrence that:

- Results in death.
- Is life threatening; (a nonlife-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the study investigator based on medical judgment (e.g., may jeopardize the study participant or may require medical/surgical intervention to prevent one of the outcomes listed above).
- The occurrence of the SAE acute kidney failure, defined as requiring temporary or permanent dialysis, will be a safety endpoint.

8.1.3 DEFINITION OF UNANTICIPATED (UNEXPECTED) PROBLEMS

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of unexpected/unanticipated problems.

The determination that a serious adverse event is related to the study treatment is initially made by the study investigator, reviewed by the medical monitor and DSMC.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Events that result in temporary or permanent discontinuation of study medication will be recorded on appropriate study eCRF (See MOP).

The intensity (or severity) of events will be rated on a three-point scale:

- **Mild**: Events that require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate**: Events that result in a low level or inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. Mild or moderates side effects to study medication may result in temporary or permanent discontinuation without being a serious adverse event.
- **Severe:** Events that interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

8.2.2 RELATIONSHIP TO STUDY AGENT

The study investigator will assess the relationship of any serious adverse event or adverse events that lead to discontinuation of study medication to be related or unrelated by determining if there is a reasonable possibility that the reported event may have been caused by the treatment. To ensure consistency of AE/SAE causality assessments, study investigators should apply the following general guideline when determining whether an AE/SAE is related:

- **Related:** There is a plausible temporal relationship between the onset of the event and administration of the study treatment, and the event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the event follows a known pattern

of response to the study treatment; and/or the event abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.

- **Not related:** Evidence exists that the event has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the event has no plausible temporal relationship to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study drug); and/or an alternate etiology has been established.

If necessary, the PCC PI or investigator will consult with CC in order to determine the relatedness of an AE/SAE.

8.2.3 EXPECTEDNESS

The PCC PIs will be responsible for determining whether of any serious adverse event or adverse events that lead to discontinuation of study medication is expected or unexpected. An AE/SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent in the package insert. If necessary, the PCC PI or investigator will consult with CC in order to determine the expectedness of an AE/SAE.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Serious adverse events (SAEs) occurring during the study period must be recorded. SAEs that are related to the study medication that are still ongoing at the end of the study period must be followed up to determine the final outcome. SAEs that occur within 30 days after study drug discontinuation will occur within the period of long-term follow-up as specified by the protocol. SAEs will be reported on a SAE form in the EDC system (see MOP).

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Each PCC PI is responsible for adhering to the oversight and safety reporting requirements of their center's Institutional Review Board or the central IRB.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Unexpected, related serious events must be reported to the CC immediately after the event comes to PCC staff attention via completion of the EDC SAE form. If the study participant required hospitalization, the hospital discharge summary must also be sent to the CC. In the event of problems with the online SAE form, the PCC PI or investigator will contact the CC. CC staff will report these events to the applicable regulatory authorities within the required timelines (see MOP for details).

Unexpected, related SAEs are reviewed by the Medical Monitor to verify the coding and the reporting that is required. These and all other reported SAEs are reviewed by the DSMC. MedDRA coding conventions will be used. The CC will notify all PCC PIs of the DSMC findings and recommendations.

8.4.3 UNEXPECTED/UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for unexpected/ unanticipated problems require the notification of the CC. It is the site investigator's responsibility to report unexpected/ unanticipated problems s to their IRB and to the CC.

To satisfy the requirement for prompt reporting, unexpected/ unanticipated problems will be reported using the following timeline:

- unexpected/unanticipated problems that are SAEs will be reported to the CC within 24 hours of the investigator becoming aware of the event.
- It is the PCC PI's responsibility to notify institutional officials and/or the IRB of unexpected/ unanticipated problems that are SAEs, as required.

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4.5 REPORTING OF PREGNANCY

Women of child bearing will have a pregnancy test prior to enrollment, if it is positive they will be ineligible for the study. If a study participant thinks she may be pregnant the study staff will request that she immediately stop the study medication and have a pregnancy test. If the pregnancy test is positive the study medication will be stopped permanently; the study participant will be referred to see her doctor and will continue to be followed by the study staff. The study investigator will notify their PCC PI who will notify their IRB and the CC within seven (7) days. The CC will notify the DSMC and FDA within fifteen (15) days.

The study investigator will have permission to follow the pregnant study participant to determine pregnancy outcome.

8.5 STUDY HALTING RULES

A formal interim analysis is proposed and is described in the SAP. In addition, a continuous sequential safety stopping rule is planned to monitor the study based on unexpected events. In this study, the predominant safety concern is acute kidney failure. The DSMC may recommend halting the study for safety, efficacy or other reasons (SAP).

8.6 SAFETY OVERSIGHT

A DSMC has been appointed by the National Eye Institute (NEI) to monitor safety unmasked to treatment at regular intervals (at least once/6months).

Safety oversight will be under the direction of the DSMC that is composed of individuals with the appropriate expertise, including ophthalmology, statistics, clinical trials and ethics. The DSMC will meet at least semiannually to assess safety and efficacy data on each group of the study. The DMSC will operate under the

rules of an approved charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data and will be written and reviewed at the organizational meeting of the DSMC. At this time, each data element that the DSMC needs to assess will be clearly defined. The DSMC will provide advice to NEI. The DSMC will monitor study participant safety and review performance of the trial. Reports will be prepared regularly in accordance with the plan outlined in the charter and as requested by the DSMC chair, and will include interim analysis(es) of primary and secondary endpoints; additional safety events; and other information as requested by the committee. After each meeting, the DSMC will give advice to the NEI about the continuation of the study. After approval by the NEI, a summary of the DSMC report and recommendations will be forwarded by the CC to investigators for submission to their local and central IRBs, as applicable. DSMC reports will be the primary mechanism for reporting safety concerns to NEI and IRBs.

Sequential safety procedures (54) for life-threatening conditions in clinical trials will be employed. The unmasked study statisticians will be responsible for the oversight and implementation of this plan. Results will be provided to the DSMC.

If study participant safety requires unmasking, such as in the event of overdose of study medication, unmasking will be available through a 24-hour helpline answered by a physician medical monitor. Procedures for this unmasking and for its documentation are described in the MOP.

9 CLINICAL MONITORING

PCC monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Monitoring for this study will be performed by ZEDS CC staff.

The CC is the first line of contact for trial PCC staff and investigators regarding current protocol and CRF versions, forms, procedures, quality, monitoring, and other study components, ensuring PCC understanding and operationalization of the protocol, and successful identification of eligible patients for screening and enrollment, protocol adherence and study participant retention. Substantial written correspondence and logs of phone conversations will be filed within the ZEDS mailbox. All IRB related correspondence will be filed in the PCC's file within the ZEDS Trial Master File (TMF).

Study recruitment, enrollment, and retention are monitored based on reports generated by the data acquisition and management system. Study screening information is reviewed by comparing the characteristics of study participants enrolled versus screened out, assisting with potential strategies to improve study enrollment. The ratio of screened to randomized participants is also reviewed. Enrollment and visit attendance is also monitored on an ongoing basis by participant, by PCC, and for the overall study.

Data performance indicators for each PCC and for the overall study are also reviewed. These include CRF-level and field-level completeness, data accuracy, data entry timeliness, query resolution timeliness. Essential protocol adherence requirements are also monitored from the database. Important components of adherence monitoring include ensuring that informed consents are signed and dated by the participant, confirming that study participants are re-consented in accordance with protocol specifications (if needed), and making sure that inclusion and exclusion criteria are met. PCCs with study participants who have excessive missed study visits, as well as data collected outside the permitted visit windows are identified, and participants who are not

adhering to protocol medication or treatment compliance requirements are identified and reported to the appropriate study personnel.

A crucial part of data integrity monitoring is the ongoing review, monitoring and cleaning of study data for completeness and accuracy. During this process CC staff reviews trends in data collection patterns across centers. Issues are flagged as they arise and resolved accordingly. The data management staff will communicate these trends and data collection issues to NEI and study monitors at the CC to ensure that monitors are aware of the issues and can appropriately review and verify PCC data.

This trial will utilize centralized, remote, and risk-based monitoring for regulatory, data and safety monitoring, along with onsite monitoring for specified source verification and risk management, for cause. Initially the PCCs have been required to provide information related to the training of the study investigator, co-investigators and coordinators, and past research experience. The centers have also been assessed to determine the extent at which they have access to electronic medical records (EMR) and to electronic data capture (EDC). If additional centers are added similar information will be obtained.

The CC will ensure the training of monitoring personnel prior to initiation of study enrollment and as specified in MOP to ensure the monitoring plan is executed. This will include but not be limited to training of monitors on specific protocol requirements, monitoring plans, and standard operating procedures.

Details of PCC monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, frequency of monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL ANALYSIS PLAN

A Statistical Analysis Plan provides a complete description of all statistical considerations and analysis plans (see SAP).

10.2 STATISTICAL HYPOTHESES

The primary objective of this randomized controlled clinical trial is to test the hypothesis that long-term suppressive antiviral treatment for 1 year with oral valacyclovir 1000 mg daily delays the time to the first occurrence of new or worsening anterior segment ocular disease (*dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis*) compared to placebo by 12 months.

The secondary objectives are (1) a) to test the hypothesis that long-term suppressive antiviral treatment for 1 year with oral valacyclovir 1000 mg daily delays the time to the first occurrence of new or worsening anterior segment ocular disease (*dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis*) compared to placebo by 18 months; and b) to test the hypothesis that the occurrence of new or worsening disease in the 6 months post treatment period is reduced for participants treated with valacyclovir compared to placebo; and (2) to test the hypothesis that suppressive treatment for 12 months with oral valacyclovir 1000 mg daily reduces the

incidence, severity and duration of post herpetic neuralgia (PHN) compared to placebo at 12 and 18 months in patients with HZO.

To evaluate these hypotheses, the following endpoints will be evaluated:

Primary Efficacy Endpoint:
The primary endpoint is the time to first occurrence of new or worsening episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, accompanied by pre-specified changes in treatment for the same disease manifestation of HZO (see MOP) during the twelve months of treatment. The primary endpoint is compared for participants randomized to study medication or placebo.

To assess the primary objectives, study participants will be monitored at each visit for new or worsening any of the following conditions (see MOP for definitions):

1. Dendriform epithelial keratitis:
2. Stromal keratitis
   a. Without ulceration
   b. With ulceration
3. Endothelial keratitis
4. Iritis

The endpoint of first occurrence of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis will be determined by clinical examination accompanied by prespecified changes in treatment (see MOP), as there are no validated confirmatory biomarkers or other tests.

Secondary Efficacy Endpoints:
To assess the secondary objectives, the study participants will be monitored at each visit for the following:

1. Time to development and number of episodes of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, requiring pre-specified changes in treatment (see MOP), during the 18 months following randomization, that includes the 6 months following cessation of treatment; and during the 6 months following the end of the 12 month treatment period.
2. The incidence, severity, and duration of PHN at one year of treatment, and after the 6 month post-treatment follow up.
3. Impact of vaccination against zoster with RZV on outcomes.
4. Development of specific manifestations of HZO, classified as dendriform epithelial keratitis, stromal keratitis (all types), endothelial keratitis, iritis requiring pre-specified changes in treatment (see MOP), neurotrophic keratopathy with or without melting and/or microbial superinfection, episcleritis, and/or scleritis during the twelve months of treatment.
5. Secondary glaucoma as determined by IOP and treatment required.

Exploratory Efficacy Endpoints:

1. Changes in strength and/or frequency of prescribed topical corticosteroids at 12 and 18 months.
2. Occurrence of stroke
3. Occurrence of temporal arteritis/giant cell arteritis
4. Occurrence of myocardial infarction

5. Occurrence of new or worsening malignancy
   a. Solid tumor (other than non-melanoma skin cancer)
   b. Hematologic malignancy
   c. Lymphoma.
6. Time to development and number of episodes of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, with a recent substantial reduction in treatment (see MOP) during 12 months of treatment.
7. Impact of suppressive antiviral treatment prior to enrollment on outcomes during 12 months of study treatment.

10.3 ANALYSIS DATASETS

All study participants who were randomized into the study will comprise the intent-to-treat population, the primary analysis population for efficacy. Study participants who received at least one dose of the assigned study drug will comprise the as-treated population, the primary analysis population for safety. Note, participants on either arm can receive off study valacyclovir or other antivirals after the primary endpoint is reached or for the occurrence of herpes simplex. During the time period that other antivirals are received, participants must be off study medication. Therefore, safety analyses will be conducted in this as-treated population until participants go off treatment at the end of the study or receive off treatment antiviral therapy for a primary endpoint or for herpes simplex. For this subset of participants who receive antiviral therapy for these reasons, additional analyses of safety for the time period following resumption of study medication will be conducted. Further supportive analyses of safety will be carried out for study participants who complete 12 months of treatment. Details provided in SAP.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

The ZEDS trial is a multicenter double-masked RCT that will enroll approximately 780 study participants with a medical record documentation of an episode of dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to Herpes Zoster that was diagnosed in the past year. Eligible study participants will be randomized via a computer IXRS system following confirmation of eligibility within PCC in 4 strata defined by age at HZO onset (less than 60 years, or 60 years and greater, at time of HZO onset) and by recent onset or chronic HZO (recent onset: HZO diagnosed within 6 months of the enrollment/ randomization visit; chronic: HZO diagnosed 6 or more months prior to the enrollment/randomization visit).

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the time from randomization to development of the first occurrence of any new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis due to HZO, diagnosed by a change in clinical slit lamp biomicroscopy examination and accompanied by prespecified changes in treatment (see MOP) by 12 months of treatment with valacyclovir compared to placebo.

The objective of the analysis of the primary endpoint is to compare cumulative failure rates (failure defined as an episode of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or

iritis) in the valacyclovir treated groups with the placebo treated group by 12 months (treatment completion). Kaplan-Meier curves will be plotted by treatment group (overall and within strata) and 95% confidence intervals (adjusted for interim analyses) for the difference between the 12-month cumulative failure rates will be estimated (overall and within strata). Results will also be plotted within strata and by baseline disease and study participant characteristics to provide descriptive summaries of the results.

The primary study analysis will be based on a stratified log-rank (2-sided) test with adjustment for stratification factors (age, and recent onset vs. chronic disease).

Details of all analyses, including sensitivity analyses are provided in the SAP. For example, analyses will be provided that incorporate adjustments of study medication to one 500 mg pill twice daily or one 500 mg pill daily instead of the standard 2 pills daily; and that evaluate the impact of study drug discontinuation by treatment group.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints are listed in Section 10.2 above. Methods for the analyses that compare these outcomes by randomized treatment group are described in the SAP.

10.4.4 EXPLORATORY ANALYSES

Exploratory analyses to compare the rates of occurrence of each of the exploratory endpoints described above will be conducted as described in the SAP.

10.4.5 SAFETY ANALYSES

All study participants who were randomized into the study will comprise the intent-to-treat population, the primary analysis population for efficacy. Study participants who received at least one dose of the assigned study drug will comprise the as-treated population, the primary analysis dataset for safety.

The analysis datasets for safety are described in Section 10.3 (Analysis Datasets) above. Details are provided in SAP.

The occurrence of acute kidney failure, defined as requiring temporary or permanent dialysis, in these patients will be monitored using a safety monitoring rule as described in the SAP and compared between the two treatment groups.

SAEs will be analyzed in a similar manner. For all safety events, the rates of study drug termination will be summarized and compared by treatment group and strata.

10.4.6 ADHERENCE AND RETENTION ANALYSES

Study recruitment, retention, and adherence will be monitored by PCC and randomization strata. For each PCC, numbers of patients screened, numbers randomized, numbers of ineligible patients, treatment compliance as measured by pill count for individual study participants, protocol deviations, timeliness of data reporting and query resolution, numbers of queries/study participant, and additional monitoring measures will

be provided by center and reviewed monthly. All results will be summarized over time using descriptive statistics, graphical displays, and frequency distributions as appropriate. Retention rates by PCC and strata will also be monitored over time.

10.4.7 BASELINE DESCRIPTIVE STATISTICS

Plans for the comparison of baseline characteristics between the two randomized treatment groups are provided in the SAP.

10.4.8 PLANNED INTERIM ANALYSES

The interim analysis plan is described in the SAP.

10.4.8.1 SAFETY REVIEW

For ethical reasons, an independent DSMC appointed by the National Eye Institute (NEI), will monitor study participant safety and review performance of the trial at regular intervals during the trial. The primary objective of these interim safety analyses is to ensure the safety of the study participants randomized in the trial. This interim monitoring will involve a review of study participant recruitment, compliance with the study protocol, status of data collection, and other factors that reflect the overall progress and integrity of the study. Formal interim analysis of efficacy will evaluate the accumulating endpoint data by treatment group. The interim monitoring plan is described in the SAP.

10.4.8.2 EFFICACY REVIEW

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Interim analysis(es) for efficacy by treatment group will focus on the primary endpoint is described in the SAP.

Judgment concerning the continuation of the study will involve not only the magnitude of observed differences between randomized strategies and degree of statistical significance, but also careful consideration of many other important factors including the need for precise parameter estimation, the overall progress and integrity of the trial including the frequency of serious adverse events associated with active study medication, and information available from other studies at the time of DSMC deliberations.

10.4.9 ADDITIONAL SUB-GROUP ANALYSES

Analyses of primary and secondary endpoints will be presented by strata, by covariates including comorbidities such as diabetes, cancer among others, and by Zoster vaccination status as well as by gender. Details are provided in the SAP. Pre-specified subgroup analyses will be provided in the SAP.

10.4.10 MULTIPLE COMPARISON/MULTIPLICITY

A statistical adjustment for interim efficacy analyses is incorporated into for the analysis of the primary endpoint. No further adjustments for multiplicity are incorporated; any adjustments for multiplicity developed for the secondary analyses for the final study protocol will be incorporated into the SAP prior to unmasking and analysis of results.

10.4.11 EXPLORATORY ANALYSES

Exploratory analyses to compare the rates of occurrence of each of the exploratory endpoints described above will be conducted as described in the SAP.

10.5 SAMPLE SIZE

The overall study sample size is based on the primary endpoint of episode of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis accompanied by pre-specified changes in treatment (see MOP) by 12 months for the ZEDS RCT as described above. On the basis of available data, the 12-month cumulative failure rate for the primary endpoint in the placebo group was estimated at 30% among study participants.

Under the assumption that the cumulative 12 month failure rate in the placebo group is 30% with approximately 390 study participants randomized to each of the two treatment groups, (including a planned interim analysis) we can detect a difference between the placebo and valacyclovir treated groups in failure rate at 12 months (treatment completion) of +/-8.7% (to 21.3% in the valacyclovir group), an approximately 30% treatment effect, with a two-sided alpha = 0.05 and 80% power (without adjustment for interim analyses) These considerations are equivalent to a detectable hazard ratio for failure on valacyclovir relative to placebo of 0.67 based on a logrank-test for the comparison of the distributions of failure times between the two groups. [Calculations from EAST 6.5, Cytel, 2018] We estimate that approximately 780 study participants can be randomized into this study over an estimated 7-year accrual period. All randomized study participants will be included in the intent-to-treat analysis to compare cumulative failure rates by 12 months (failure time is defined as from randomization to the development of first episode of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, and/or iritis) in the valacyclovir arm and placebo arm. [ZEDS SAP provides a complete description of the approach].

Sample size may be re-estimated using aggregate event rates as described in the SAP.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Eligible study participants will be randomized centrally using the IXRS web-based interactive computerized system (see MOP). Study participants will be randomized following confirmation of eligibility by the system within center in the four strata, defined by age at onset of HZO (less than 60 years or 60 years and greater) and by recent onset or chronic HZO (recent onset defined as HZO diagnosed within 6 months of enrollment/ randomization, or chronic defined as HZO diagnosed 6 months or more prior to enrollment/randomization). The IXRS system allows PCC staff to log in and obtain the masked randomization assignment and supply assignment for individual study participants after on-line confirmation of eligibility and informed consent is obtained. The IXRS will provide electronic files with randomization numbers to the DCC for supply labeling prior to sending supplies to centers. Confirmation of eligibility and randomization and supply assignments are then incorporated into the) Electronic Data Capture clinical trials database and become part of the study files.

Note that all data management staff in the CC are masked to treatment assignments throughout the study process. The only exceptions to this are the unmasked statisticians.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

A 24-7 helpline will be available for unmasking by the medical monitor in the event of a medical emergency that requires unmasking for the safety of the study participant. (See MOP)

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each PCC will maintain appropriate medical and research records for this trial, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participants.

Source documents contain source data and include medical records, paper CRFs and images and all other information necessary to reconstruct and evaluate the clinical trial (see MOP).

The study investigators will permit study-related monitoring, audits, and inspections by the IRB, the NEI, government regulatory agencies, and NYULMC staff of all study-related documents and the capability for inspections of study-related facilities.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., regulations of the National Eye Institute of the National Institutes of Health (NEI/NIH), the Food And Drug Administration (FDA) and the International Council for Harmonisation (ICH)).

The PCCs will provide direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the CC, NEI, and inspection by local and regulatory authorities.

See MOP for details on QA and QC processes.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

This study is to be conducted in accordance with applicable US government regulations and institutional research policies and procedures. The protocol and any amendments will be submitted to a properly constituted Central Institutional Review Board (CIRB) or, as required, to IRBs at PCCs for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the study investigators and a copy of this decision will be provided to the CC before commencement of the study. Annual renewals will be submitted to the CC.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any study participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Withdrawal of IRB Approval
A study investigator shall report to the CC a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to any study-related activities taking place.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Written informed consent will be obtained from all potential study participants on an approved consent form. Potential study participants will be provided sufficient information to make an informed decision about their participation in the study. The investigator will explain the research study to the potential study participant and answer any questions that may arise. All potential study participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Potential study participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The potential study participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The formal consent of a study participant, using the IRB approved consent form, must be obtained before that study participant undergoes any study procedure. The consent form must be signed and dated by the study participant and the study investigator-designated research professional obtaining the consent. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

A study participant informed consent form has been approved by the NYUSoM IRB. This consent form will be submitted with the protocol for review and approval by CIRB or the IRB at the PCCs for this study. Any changes made to the informed consent form at the PCCs will be reviewed by the CC staff.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

To protect against the risk of loss of confidentiality, the study will follow the procedures specified by the NYULMC IRB, central IRB or IRBs of the PCCs. Study participants will be assigned a unique identification number using no identifying information. Personal identifying information such as name, address, driver's license, or Social Security Number will not be entered into the database. The CC at NYULMC is IRB approved and has experience in managing PHI and are extremely prudent in keeping study participant data secure and confidential through a number of standard operating procedures. Transmission of informed consent forms and records with any PHI for central source document verification by CC monitors will occur by SafeSend email, or secure fax, or mail. The control of access to databases will be managed centrally by the CC through user passwords linked to appropriate access privileges. This protects data from unauthorized view and modifications and from inadvertent loss or damage. The CC has an extensive data security infrastructure. Materials that contain PHI will be stored securely at PCCs. This information will be retained by each individual center and will not be entered into the any of the study databases. If a PCC closes and cannot continue to follow enrolled participants, they may be transferred, with the study participant's consent, to another PCC.

Information about study participants will be managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA), including obtaining written authorization to collect and use protected health information (PHI). In the event that a study participant revokes authorization to collect or use PHI, the study investigator retains the ability to use all information collected prior to this revocation. In this situation, the study investigator should attempt to obtain permission to collect at least information that the study participant is alive at the end of their scheduled study period.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Not applicable.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

PCC staff will be trained in the proper collection, storage and transmission of study data. All established procedures will be readily available to PCCs in the MOP. Informed consent forms and all source documents with PHI to be stored with any study records must be in a double-locked secure location and/or password

protected, encrypted electronic files at each PCC in compliance with local IRB PHI will be redacted before submission for central monitoring (see MOP and SAP).

CC staff will provide the PCC staff with a visit checklist to ensure that all required data are collected at each visit and in the preferred order of data collection. A secure, compliant, web based electronic data capture (EDC) system will be developed to process, edit and store all study data in a centralized database. PCC staff will document relevant information on source documents and enter data into the EDC system. A comprehensive data management methodology will be implemented. All data will be reviewed for completeness, accuracy and logical consistency though out the duration of the study. Final data cleanup will be completed shortly after the last study participant visit, at which time the study database will be locked and provided to the study statistician for analyses.

14.2 STUDY RECORDS RETENTION

It is the study investigator's responsibility to retain all study documents in accordance with federal regulations and any applicable local state and institutional requirements after the investigator has been informed by the CC that the study analyses have been completed and the study has been closed.

14.3 PROTOCOL DEVIATIONS

Protocol Deviations:
A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or MOP requirements. The noncompliance may be on the part of the study participant, the investigator, or PCC study staff. As a result of deviations, corrective actions are to be developed by the PCC and implemented promptly.

These practices are consistent with ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study participant's source documents and promptly reported within the EDC system. Protocol deviations must be reported to the PCC's responsible IRB per their guidelines and the DSMC at each review. Further details about the handling of protocol deviations are included in the MOP.

14.4 PUBLICATION AND DATA SHARING POLICY

The Publications Committee will authorize access to study data.

All data access will follow guidelines described in the NIH Data Sharing Policy (http://grants.nih.gov/grants/gwas/index.htm), the Food and Drug Administration Amendments Act of 2007 (FDAAA), and ClinicalTrials.gov.

The Study Chair, Study Co-Chair and PIs of the CC at NYULMC have the primary responsibility for the publication of the results of the study. The DSMC will review the report of the primary results of the study prior to submission for publication.

Any PCC investigator involved with this study is obligated to provide the sponsor (NYULMC) with complete test results and all data derived from the study. Primary and secondary reports of study findings will be published in peer-reviewed journals. Proposals for presentations and publications incorporating study data must be submitted for review by the publications committee.

No PCC investigator is permitted to present or publish data obtained during the conduct of this trial without prior approval from the publications committee. PCC investigators must submit a proposal requesting access to trial data.

The full publications policy may be found in the MOP.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study is sponsored by the US National Eye Institute. The Study Chair and Study Co-Chair, supported by the CC maintain responsibility for the overall conduct of the study, including site management and site monitoring analysis and reporting. The Statistics and Data Management Leadership is responsible for the receipt and processing of data collected by the PCCs, quality control programs, and statistical analysis and reporting. Members of the NEI will participate in the study leadership. Details regarding the CC may be found in the MOP.

Details of the Committees, e.g. Executive Committee and Clinical Event Review Committee, their charge, and membership may be found in the MOP.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NEI has established policies and procedures for all study group members to disclose all conflicts. Details are in the MOP.

17 LITERATURE REFERENCES

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APPENDIX

Version	Date	Significant Revisions
1.0	March 10, 2017	Original release
1.1	August 7, 2017	Clarification of the use of divided dose and reduced dose of the study medication. Correction of the Schedule of Events table.
2.0	February 12, 2018	Clarification of secondary endpoints 1 and 3. Addition of new exploratory endpoint. Clarification of inclusion criterion 6. Clarification of exclusion criterion 5 to include usually vesicular rash. Clarification of exclusion 6 to include use of the new zoster vaccine and temporary discontinuation of study medication when study participant takes the new vaccine. Clarification of the discontinuation of study medication when study participant develops a contraindication to valacyclovir. Clarification of the discontinuation of study medication due to use of open label antiviral medication. Correction of the use of participant diaries. Clarification of the review of SAEs by medical monitors and the DSMC.