M-1-(1) Scientific Abstract

Age-related macular degeneration (AMD) is the second most common cause of vision loss among adults in developed countries, the first being diabetic retinopathy. There are approximately 1.7 million people in the USA who have impaired vision due to AMD, a number that is expected to triple by the year 2030 as the population ages. Every year in the USA more than 165,000 people develop AMD, and 16,000 become legally blind with a visual acuity of less than 20/200, predominantly from the rapidly progressing 'wet' form of the disease [1]. Wet AMD, which is the lay term for neovascular AMD, is characterized by growth of new vessels into the normally avascular subretinal space and photoreceptor layer, a process called choroidal neovascularization (CNV). The new vessels are leaky resulting in subretinal and intraretinal fluid that reversibly reduces visual acuity. Over time, CNV recruits cells resulting in scarring that causes permanent damage and loss of central vision. Vision is often reduced to 20/200 or worse which is the definition of legal blindness and is debilitating because legal blindness in both eyes makes it impossible to read, drive, recognized faces, and often results in loss of independence. Depression is a frequent result of advanced, bilateral AMD.

Therapies using intravitreal injections of anti- Vascular Endothelial Growth Factor (VEGF) drugs such as ranibizumab (Lucentis) and bevacizumab (Avastin) have been efficacious in many patients with 68% of patients gaining some vision[2]. However, these therapies require monthly or six-weekly intravitreal injections and continued monthly treatment provides superior outcomes to intermittent treatment based upon evidence of recurrent disease. Monthly visits and frequent injections are a substantial burden on patients and the greater the number of injections, the greater the risk of endophthalmitis. Consequently, there is a need for alternative longer-term therapies that avoid the risks associated with frequent and costly intravitreal injections.

The proposed therapeutic, RetinoStat®, is a minimal non-replicating, recombinant lentiviral vector derived from the non-primate lentivirus Equine Infectious Anaemia Virus (EIAV). RetinoStat® is designed to express human endostatin and angiostatin, two proteins with well known broad-range anti-angiogenic actions. Whilst RetinoStat® is able to transduce many cell types, the anatomical separation of the eye from the rest of the body limits the ability of RetinoStat® injected subretinally to affect tissues other than the eye. The continual local secretion of endostatin and angiostatin from the RetinoStat® transduced retina is expected to result in chronic long-term suppression of the neovascular stimulus.

In a murine disease model (the laser-induced CNV model) significant inhibition (49%) of the area of the CNV lesion was observed following subretinal injection of murine RetinoStat® at 6.2×10^5 TU/eye. We have also observed that following subretinal delivery (3.2×10^6 to 5.6×10^7 TU/eye) reporter (GFP) expression can be detected as early as 3 days and persists for at least 16 months in the mouse. In six-month toxicology studies in Rhesus macaques and rabbits a dose of 1.1×10^5 TU/eye caused no adverse effects and was well-tolerated with respect to the inflammatory response.

The proposed clinical trial is an open-label, dose-escalation, phase I study to investigate the safety and tolerability of subretinally injected RetinoStat® in patients with advanced wet AMD and subretinal fibrosis. RetinoStat® will be injected once subretinally into the most severely affected eye that must present with active leaking CNV. Patients will be aged 50 or above and have a best corrected vision of 20/200 or worse in the eye to be treated. Three ascending dose levels of RetinoStat® will be

assessed for safety and tolerability. A secondary endpoint is t o evaluate the biological activity of RetinoStat®.

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[1] Department of Health and Human Services, National Eye Institute, Age-Related Macular Degeneration. Status of Research, Harold Varmus, March 1997.

[2] Rosenfeld PJ et al Ranibizumab for neovascular age-related macular degeneration.; MARINA Study Group.N Engl J Med. 2006 Oct 5;355(14):1419-31.