LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 2
1 GENERAL INVESTIGATIONAL PLAN 3
1.1 Rationale for the Clinical Development of Latanoprost-Dorzolamide Ophthalmic Solution 3
1.2 Indications to be Studied 6
1.3 General Evaluative Approach 6
1.4 Types of Clinical Trials Planned 7
1.5 Number of Subjects to be Treated 7
1.6 Anticipated Clinical Risks 7
REFERENCES 9

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AGIS	Advanced Glaucoma Intervention Study
BCVA	best-corrected visual acuity
BID	twice daily
FDA	Food and Drug Administration
IND	Investigational New Drug
IOP	intraocular pressure
OAG	open-angle glaucoma
OHT	ocular hypertension
QD	once daily
QID	four times daily
SAE	serious adverse event
SD	standard deviation
TID	three times daily
US	United States

1 GENERAL INVESTIGATIONAL PLAN

1.1 Rationale for the Clinical Development of Latanoprost-Dorzolamide Ophthalmic Solution

In the US population, glaucoma is a leading cause of visual field damage, including loss of peripheral vision, depth perception, and contrast sensitivity. It is also the second leading cause of blindness worldwide (McKinnon, 2008; Whitson, 2007). The Eye Diseases Prevalence Research Group estimates that open-angle glaucoma (OAG) afflicts 1.86% of adults ages 40 and older and approximately 2.2 million US citizens in total. This total is forecast to increase by 50% by the year 2020, affecting approximately 3.3 million US citizens, due in large part to the number of adults transitioning to upper age brackets (American Academy of Ophthalmology, 2005; Friedman, 2004). Recent clinical findings provide evidence that patients with OAG are most likely to be protected from progressive loss of sight when intraocular pressure (IOP) is reduced to the maximum extent possible. Data analyses conducted by the Collaborative Initial Glaucoma Treatment Study and the Advanced Glaucoma Intervention Study (AGIS) support this concept, asserting that aggressive IOP reduction is vital for preventing degradation in optic nerve function and visual field loss (AGIS Investigators, 2000; Lichter, 2001). These findings, along with increasingly efficacious ocular hypotensive medications, are resulting in updated treatment standards that are considerably more aggressive than prior standards of care (AGIS Investigators, 2000; Noecker, 2006).

Applying a topical hypotensive medication with a single active ingredient is a strategy that remains primary for treating patients newly diagnosed with OAG or ocular hypertension (OHT), yet this strategy is frequently ineffective at reducing IOP to the extent necessary to protect the visual field; approximately half of all glaucoma patients require treatment beyond a single drug therapy (Tamer, 2007). When monotherapy does not sufficiently lower IOP, physicians often supplement the existing treatment with other ocular hypotensives. Two ocular hypotensive therapies that have the demonstrated the ability to produce an additive increase in IOP reduction when administered simultaneously are latanoprost 0.005% and dorzolamide 2.0%. Clinical studies have shown the simultaneous administration of latanoprost 0.005% and dorzolamide 2.0% to be safe and effective for providing reduction in IOP beyond what can be achieved by these drugs independently (Arici, 1998; Maruyama, 2006; O'Connor, 2002; Tamer, 2007).

Intraocular pressure is a result of the production of aqueous humor by the ciliary body in conjunction with the removal of aqueous humor through the trabecular meshwork and the sclera. Latanprost and dorzolamide influence this system, each through a unique mechanism of action, to reduce raised IOPs to safe levels. Latanoprost 0.005%, a prostaglandin $F_{2\alpha}$ analog, is marketed in the United States by Pfizer under the trade name Xalatan®. Both nonclinical and clinical studies show that latanaprost reduces pressure in patients with raised IOPs by increasing the outflow of aqueous humor through the uveoscleral outflow pathway (Pfizer, 2006). Dorzolamide 2.0% is a carbonic anhydrase inhibitor marketed in the United States by Merck and Co, Inc. as an ophthalmic solution under the trade name Trusopt®.

Dorzolamide reduces IOP via the inhibition of carbonic anhydrase. Carbonic anhydrase catalyzes the reversible reactions of the hydration of carbon dioxide or the dehydration of carbonic acid. Carbonic anhydrase is suppressed in the ciliary processes, slowing the formation of bicarbonate ions and resulting in decreased sodium and fluid transport, thus decreasing aqueous humor formation and leading to a reduction in IOP (Merck, 2008).

Since receiving approvals in the US, latanoprost 0.005% and dorzolamide 2.0% have been clinically evaluated for additive effect in IOP reduction when dosed concomitantly; the following represent a few of these studies.

- **Additive Effect of Latanoprost and Dorzolamide in Patients With Elevated Intraocular Pressure (Arici, 1998)**

In a 20-day, randomized, observer-masked, parallel-group, crossover study, 30 patients ages 40 years and older with elevated IOP (≥22 mm Hg in at least 2 independent measurements) due to OHT or early capsular or primary OAG were randomly assigned 1:1 to parallel treatment groups. The study regimen consisted of 2 consecutive treatment periods of 10 days each. The first group of 15 patients received latanoprost dosed once daily (QD) during the initial 10 days, then added dorzolamide dosed TID to the treatment regimen during the second 10 days. The second group of 15 patients received dorzolamide dosed TID for the first 10 days, then added latanoprost dosed QD to the treatment regimen during the second 10 days.

During the 20 day period, both groups experienced significant IOP reductions from baseline at all time points. The IOP lowering effects of monotherapy in each group were evident by Day 2. On Day 10, the mean IOP measurement for Group 1 (latanoprost only) was 30.2% lower than baseline ($P<0.01$) and 19.4% lower than baseline ($P<0.01$) for Group 2 (dorzolamide only). After 10 days of combined administration of latanoprost and dorzolamide (Days 11 – 20), IOP measurements at Day 20 revealed a mean IOP for each group that was significantly less than Day 10; Group 1 had a 15% reduction from Day 10 ($P<0.01$) and Group 2 had a 24.1% reduction from Day 10 ($P<0.01$).

- **The Hypotensive Ocular Effect Produced by the Association of Latanoprost With Dorzolamide (Chiselita, 1999)**

In a 14-day study in patients with primary open-angle glaucoma, 32 affected eyes were dosed with either latanoprost or dorzolamide for the initial 7 days, resulting in Day 7 mean IOP reductions from baseline Day 0 of 28% and 19.8%, respectively. Latanoprost and dorzolamide then were administered concomitantly to the same 32 eyes for the remaining 7 days, producing Day 14 average IOP reductions from baseline Day 0 ranging from 37% to 39% .

A second stage of this same study further evaluated simultaneous dosing of latanoprost and dorzolamide over a 90-day period in second set of patients (42 eyes) representing various forms of glaucoma. Weekly IOP measurements and secondary assessments were carried out over 3 months, resulting in an average IOP reduction from baseline of approximately 30%,

regardless of glaucoma type; these reductions were achieved within the first 30 days and maintained to Day 90.

Adverse events (AEs) that occurred during the course of treatment, such as conjunctival hyperemia, burning sensation, and itching, were mild to moderate and did not effect treatment continuation. No serious AEs were reported.

- **Additive Effect of Dorzolamide or Carteolol to Latanoprost in Primary Open-angle Glaucoma - A Prospective Randomized Crossover Trial (Maruyama, 2006)**

In a 9-month prospective open-label randomized crossover clinical study, 64 patients with primary OAG were treated with latanoprost 0.005% 4 times daily (QID) for 3 months (. Then the patients were randomized 1:1 to continue latanoprost while adding either dorzolamide 1% 3 times daily (TID) or carteolol hydrochloride 2% twice daily (BID) to the treatment for a further 3 months. For the last 3 months of the trial, all patients were crossed over to the opposite concomitant therapy treatment arm. IOP measurements were recorded at baseline and at each monthly study visit.

Subjects on the latanoprost plus dorzolamide regimen during the second 3-month period of the study (Months 3–6) had a mean IOP measurement (± standard deviation [SD]) at baseline of 19.0 ± 2.1 mm Hg, 16.0±2.1mm Hg at the end of latanoprost monotherapy at Month 3, and 15.0±1.3mm Hg during concomitant therapy of latanprost and dorzolamide at Month 6. Subjects on the latanoprost plus dorzolamide regimen during the third 3-month period of the study (Months 6–9) had a mean IOP measurement at baseline of 19.0 ± 1.9 mm Hg, 16.2±1.2mm Hg at the end of latanoprost monotherapy at Month 3, and 15.2±1.5 mm Hg during concomitant therapy of latanprost and dorzolamide at Month 9.

- **Comparison of Twice-Daily and Three-Times-Daily Dosing of Dorzolamide in Ocular Hypertension and Primary Open-Angle Glaucoma Patients Treated with Latanoprost (Lupinacci, 2008)**

In a prospective, two-period crossover trial, reductions in IOP were compared between dorzolamide administered BID and TID when added to latanoprost baseline treatment. Fifteen patients (29 eyes) with primary OAG or OHT, IOPs of >20 mm Hg, and on an established latanoprost 0.005% regimen were randomized to receive also either BID or TID dosing of dorzolamide 2% for 4 weeks. After completing 4 weeks, all patients participated in a 3 week washout period in which they received only latanoprost 0.005%. Following completion of the washout period, all patients were switched to the opposite dorzolamide 2.0% treatment arm for the last 4 weeks of the study. Diurnal IOP measurements were collected every 2 hours between 8:00 am to 8:00pm at baseline and at the end of each treatment period.

Data from this study showed mean IOP measurements at baseline of 20.5 mm Hg and 21.3 mm Hg prior to BID and TID dosing of dorzolamide, respectively. At the end of 4 weeks, after having added dorzolamide 2.0% BID or TID to the existing latanoprost treatment, mean IOP measurements were 17.7±0.6 mm Hg (a 13.5% reduction) and 17.8±0.8 mm Hg (a 16.5% reduction), respectively. In both the BID and TID dosing regimens, results were

significant when compared to the baseline IOP ($P<0.001$). Further, diurnal IOP control was comparable for BID and TID treatment at all time points with the exception of 6:00 pm, when the difference in IOP reduction for TID treatment (-4.7±3.3 mm Hg) and BID treatment (-2.3±2.7 mm Hg) was significant ($P=0.038$).

While concomitant use of topical ocular hypotensives is shown in studies to be safe and effective for aggressive IOP reduction, therapeutic maintenance is equally vital for visual field preservation (American Academy of Ophthalmology, 2005). Effective maintenance depends upon the patient's ability to successfully manage the various aspects of his/her treatment, such as the dosing regimen, the refill schedule, and the monetary costs of multiple medications. The patient's age and the overall number of medications he/she is taking (not limited to ophthalmic) are also factors that affect therapeutic adherence (Noecker, 2006, Whitson, 2007). These complexities, among others, have contributed to a high rate of treatment noncompliance among those with OAG and OHT (Gurwitz, 1993; Olthoff, 2005). Adherence categorized as "relatively poor" has been noted in one-third or more of these patients, depending upon the medications prescribed (American Academy of Ophthalmology, 2005).

With all of these considerations in mind, Sirion Therapeutics is developing and studying the efficacy and safety of ST-802, latanoprost-dorzolamide ophthalmic solution. ST-802 will combine latanoprost 0.005% and dorzolamide 2.0%, active drugs that have approval individually as topical ophthalmic pharmaceuticals for IOP reduction, into a single topical ophthalmic product. Ideally, combining latanoprost 0.005% and dorzolamide 2.0%, each having a different mechanism of action, will provide patients with the advantage of enhanced IOP reduction while potentially improving therapeutic compliance via a more convenient dosing regimen. Furthermore, the novel vehicle formulation of ST-802 allows room temperature storage of the product,eliminating the need for the patient to keep the product refrigerated, as other latanoprost products have, to this point, required.

1.2 Indications to be Studied

The indication to be studied is the reduction of intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension.

1.3 General Evaluative Approach

Latanoprost and dorzolamide are approved drug products, each with an established history of effective and safe administration. Further, results from clinical crossover studies have demonstrated that concomitant dosing of latanoprost and dorzolamide is safe and more effective than dosing either product alone (see Section 1.1). On this basis, Sirion seeks to conduct a Phase 2 proof of concept study designed to compare the safety and efficacy of a single latanoprost-dorzolamide combination product (ST-802) dosed once per day (QD) to latanoprost 0.005% dosed QD. The planned sample size for the study is 30 subjects per group, and all subjects will have a diagnosis of primary open-angle glaucoma or ocular

hypertension. The Phase 2 proof of concept trial will provide key information for consideration in the development of a Phase 3 program for ST-802.

Upon completion of the Phase 2 study, an end-of-Phase 2 meeting will be held with the Food and Drug Administration (FDA) to discuss a Phase 3 program development plan for the support of a new drug application.

1.4 Types of Clinical Trials Planned

The proposed Phase 2 trial (ST-802-001) is designed to evaluate the latanoprost-dorzolamide combination product ST-802 as a treatment for the reduction of intraocular pressure in patients with open-angle glaucoma and ocular hypertension. In the trial, 60 subjects will be randomized 1:1 to receive either ST-802 or latanoprost, 0.005% QD for 2 weeks. The primary efficacy endpoint will be the between group comparison of the mean change from baseline in IOP at the Day 14 evening visit, 22 hours after the final instillation of the study drug. Secondary endpoints will be between group comparisons of the mean change from baseline in IOP at all other study time points. Safety and tolerability data will be collected following the first instillation of the study drug, and assessments will include IOP measurement, slit lamp examination, grading of anterior chamber cell count, grading of anterior chamber flare, ophthalmoscopy, best-corrected visual acuity (BCVA), and the recording of adverse events (AEs). Study results will be used to provide necessary data for estimating sample size, identifying appropriate endpoints, and aiding the overall design of a subsequent Phase 3 development program.

1.5 Number of Subjects to be Treated

A total of 60 evaluable subjects will be enrolled at approximately 10 clinical sites in the US and randomized 1:1 to either ST-802 or latanoprost, 0.005% QD for 2 weeks.

1.6 Anticipated Clinical Risks

The population in the Phase 2 study will be comprised of males and females ≥2 years of age on the day of consent. The treatment period, 2 weeks, has been selected to provide rapid and effective control of ocular hypertension. The protocol specifies that safety and efficacy procedures are to be conducted by the investigator at each study visit to ensure adequate control of ocular hypertension.

Both latanoprost ophthalmic solution, 0.005% (Xalatan) and dorzolamide ophthalmic solution, 2% (Trusopt) have been marketed in the United States since 1996 and 1994, respectively, as treatments for elevated IOP in patients with ocular hypertension or open-angle glaucoma. The AE profiles associated with the monotherapeutic use of each drug are well documented; most AEs reported for each drug have been mild to moderate in severity (Pfizer, 2006; Merck, 2008).

In three 6-month, multi-center, double-masked, active controlled trials in which patients were treated with Xalatan, AEs reported in 5%–15% of patients were blurred vision, burning and

stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy. Local conjunctival hyperemia was also observed, however, less than 1% of the patients required discontinuation of therapy because of intolerance to conjunctival hyperemia. In 1%–4% of patients, AEs included dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia. Extremely rare events of retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy were reported (Pfizer, 2006). In patients experiencing iris darkening (browning), increase in brown iris pigment has not been shown to progress beyond discontinuation of treatment, but the resultant color change may be permanent.

In clinical trials in which patients were administered Trusopt, the most frequent AEs ocular burning, stinging, or discomfort immediately following ocular administration (approximately one-third of patients). Approximately one-quarter of patients noted a bitter taste following administration. Superficial punctate keratitis occurred in 10%–15% of patients and signs and symptoms of ocular allergic reaction were reported in approximately 10% of patients. Events occurring in approximately 1%–5% of patients were conjunctivitis and lid reactions, blurred vision, eye redness, tearing, dryness, and photophobia. Also, the following AEs have occurred either at low incidence (<1%) during clinical trials or have occurred in clinical practice where the events were reported voluntarily from a population of unknown size; frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, and/or possible causal connection to dorzolamide treatment: signs and symptoms of systemic allergic reactions including angioedema, bronchospasm, pruritus, and urticaria; dizziness, paresthesia, ocular pain, transient myopia, choroidal detachment following filtration surgery, eyelid crusting, dyspnea, contact dermatitis, epistaxis, dry mouth and throat irritation (Merck, 2008).

Results of clinical trials dosing latanoprost and dorzolamide concurrently have shown overall AEs to be similar to those in the known safety profiles of each product (Arici, 1998; Chiselita, 1999; Tamer, 2007). Accordingly, it is foreseen that the AEs resulting from the use of ST-802 will not differ substantially from the known AE profiles currently associated with latanoprost 0.005% and dorzolamide 2.0% as individual therapies.

Given (A) the proposed patient population (no pregnant or lactating females, no subjects with allergies to sulphonamides, carbonic anhydrase inhibitors, or benzalkonium chloride), (B) the severity of the diseases to be treated (OAG and OHT), and (C) the safety precautions to be implemented during the course of this proof of concept study (efficacy and safety assessments to be performed weekly on Days 0, 7 and 14 at both the morning and evening visits [12 hours apart] of each study time points), the Sponsor believes that the current preclinical and clinical safety data support the this proposed clinical study for ST-802.

REFERENCES

AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration.The AGIS Investigators. Am J Ophthalmol 2000 Oct;130(4):429-40.

American Academy of Ophthalmology Glaucoma Panel-Preferred Practice Patterns Committee. Primary Open-Angle Glaucoma. 2005.

Arici M, Topalkara A, Guler C. Additive effect of latanoprost and dorzolamide in patients with elevated intraocular pressure. Int Ophthalmol 1998;22(1):37-42.

Chiselita D, Apatachioae I, Poiata I. [The ocular hypotensive effect of the combination of latanoprost with dorzolamide]. Oftalmologia 1999;46(1):39-45.

Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, et al. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol %2004 Apr;122 (4):532 -8 2004;(4:532-8).

Gurwitz JH, Glynn RJ, Monane M, Everitt DE, Gilden D, Smith N, et al. Treatment for glaucoma: adherence by the elderly. Am J Public Health %1993 May ;83 (5):711 -6 1993;(5:711-6).

Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001 Nov;108(11):1943-53.

Lupinacci AP, Netland PA, Fung KH, Evans D, Zhao Y. Comparison of twice-daily and three-times-daily dosing of dorzolamide in ocular hypertension and primary open-angle glaucoma patients treated with latanoprost. Adv Ther 2008 Mar;25(3):231-9.

Maruyama K, Shirato S. Additive effect of dorzolamide or carteolol to latanoprost in primary open-angle glaucoma: a prospective randomized crossover trial. J Glaucoma 2006 Aug;15(4):341-5.

McKinnon SJ, Goldberg LD, Peeples P, Walt JG, Bramley TJ. Current management of glaucoma and the need for complete therapy. Am J Manag Care 2008 Feb;14(1 Suppl):S20-S27.

Merck. Trusopt Package Insert. 7-1-2008. Merck.

Noecker RJ. The management of glaucoma and intraocular hypertension: current approaches and recent advances. Ther Clin Risk Manag %2006 Jun ;2(2):193 -206 2006;(2:193-206).

O'Connor DJ, Martone JF, Mead A. Additive intraocular pressure lowering effect of various medications with latanoprost. Am J Ophthalmol 2002 Jun;133(6):836-7.

Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. Ophthalmology 2005 Jun;112(6):953-61.

Pfizer. Xalatan Package Insert. 11-1-2006.

Tamer C, Oksuz H. Circadian intraocular pressure control with dorzolamide versus timolol maleate add-on treatments in primary open-angle glaucoma patients using latanoprost. Ophthalmic Res 2007;39(1):24-31.

Whitson JT. Glaucoma: a review of adjunctive therapy and new management strategies. Expert Opin Pharmacother 2007 Dec;8(18):3237-49.