(11.2% [18/161]). Across studies, ST-605 treatment was judged by investigators to be "very satisfactory" more often than acyclovir 3% treatment (ST-605, 50.3% [81/161] vs acyclovir 3%, 44.6% [70/157]).

2.5.4.8.1 Efficacy in Special Populations

No studies were performed specifically to analyze the responses of the drug in special populations.

2.5.4.9 Onset of Action

The onset of action of ganciclovir is determined by the time of the viral replication cycle. Within a few minutes after application, the ganciclovir found in ST-605 is available to disrupt the formation of new herpes virus DNA.

2.5.4.10 Maintenance of Long-Term Benefit

The drug was effective for the duration of treatment in the clinical studies. Long-term effectiveness was not evaluated for the clinical studies. The duration of treatment for the subjects in these trials was no longer than 21 days for the subjects with dendritic ulcers and 35 days for the subjects with geographic ulcers.

2.5.4.11 Efficacy Conclusions

ST-605 (ganciclovir 0.15%) is a topical ophthalmic antiviral that has been investigated in 4 adequate and well controlled clinical trials at multiple clinical investigative sites in Africa, Europe, and Asia for the treatment of acute herpetic keratitis. ST-605 was found to be effective in the treatment of acute herpetic keratitis, as reflected by similar ulcer recovery rates and time to recovery to that of topical ophthalmic acyclovir 3%.

The results of the ST-605 clinical studies provide evidence of the efficacy of the drug for the proposed indication and dosing regimen. The proposed indication for ST-605 is for the treatment of acute herpetic keratitis (dendritic and geographic ulcers), and the proposed dosing regimen is 1 drop 5 times per day until the corneal ulcer heals and then 1 drop 3 times a day for 7 days.

2.5.5 OVERVIEW OF CLINICAL SAFETY

2.5.5.1 Safety Evaluation

A total of 7 clinical studies have been conducted with ST-605 for the treatment of acute herpetic keratitis—three Phase 2 studies (Studies 4, 5, and 6) and one Phase 3 study (Study 7), along with 2 pharmacokinetic studies with healthy subjects (Studies 2 and 3) and one pharmacokinetic study with subjects with acute herpetic keratitis (Study 1)(Table 1). All of these studies were conducted outside the US and enrolled a total of 16 healthy subjects and 377 subjects with acute herpetic keratitis. The studies were conducted with subjects in France, Madagascar, Mali, Pakistan, Senegal, Switzerland, Tunisia, and the United Kingdom.

These studies have a heterogeneous population that is reflective of the multiracial, multiethnic US population, therefore supporting generalization of the results to the US.

The principal objective of the 4 randomized, multicenter, comparative clinical trials (Studies 4, 5, 6, and 7) was to evaluate the therapeutic safety and efficacy of ST-605 on dendritic or geographic corneal ulcers in subjects with acute herpetic keratitis, relative to topical acyclovir 3%, with recovery of the ulceration as the primary endpoint. The objectives of the 3 pharmacokinetic studies were as follows (2.7.2.1.5): to determine the concentration of ganciclovir in plasma after 11 to 15 days of ST-605 treatment in subjects with acute herpetic keratitis (Study 1); to determine the concentration of ganciclovir in tears after repeated administration of ST-605 in healthy volunteers (Study 2); and to compare the local ocular tolerance of ST-605 with that of its vehicle after repeated administration in healthy volunteers; blood for ganciclovir levels was also evaluated after dosing on Day 7 (Study 3).

The dosing regimen for ST-605 was the same in Studies 4, 5, and 7 (ie, 5 times per day until the ulcer healed, then 3 times per day for 7 days), which corresponds with the dosing regimen that is proposed for ST-605. Study 6 maintained dosing at 5 times per day for 10 days. Because of the formulation differences between ST-605 gel and acyclovir 3% ointment, double-masked studies were not possible at most sites (2.7.3.5.2.2). However, investigator masking was achieved in Study 6 and at the largest enrolling site in Study 5. Furthermore, for Study 6, photographs were used to assess the healing of the ulcer and were read in a masked manner.

The presentation of AEs is drawn from 2 sources: the clinical study reports for all 7 clinical studies and the electronic data sets provided by Laboratoires Théa for the 4 clinical safety and efficacy studies that were subsequently analyzed by the Sponsor (2.7.4.4). The safety and tolerability AEs that were treatment-emergent and not due to disease progression were blurred vision, eye irritation, punctate keratitis, conjunctival hyperaemia, erythema of the eyelid, corneal disorders, and dacryostenosis acquired (2.7.4.4.4). For events such as blurred vision and eye irritation, the descriptive statistics reported in this submission utilized the electronic data sets provided by Laboratoires Théa to determine the proportion of subjects who reported these events at any time during the study and at each visit. Analyses that present efficacy results by study day with last observation carried forward (LOCF) do not carry forward baseline data. Tolerability results exclude Day 0 findings (only Study 6 actually collected Day 0 values). The safety analysis utilizes the intent-to-treat population; ie, any subject who received at least one dose of any test article. The AE data from the 3 pharmacokinetic studies were not integrated with the safety data from the 4 clinical efficacy and safety studies (2.7.4.4.1).

There were no SAEs and no deaths reported for any of the clinical trials. There were only 2 reports of systemic AEs (2.7.4.7.1), which was expected because of the very low systemic absorption of ganciclovir into circulation. Dysgeusia was reported by a single subject treated with ST-605 as "taste in mouth" in Study 7. There were no withdrawals of subjects due to AEs in Studies 4, 5, and 6 (2.7.4.6.2). In Study 7, 2 subjects treated with ST-605 and 1 subject treated with acyclovir 3% were withdrawn due to AEs (2.7.4.6.2).

ST-605 has been approved in over 30 countries for the treatment of acute herpetic keratitis and is marketed under the brand name, Virgan (2.7.4, Table 5). Virgan was launched in 1996, and 1.1 million units were sold between 1996 and March 2008. No actions have been taken relating to safety by Laboratoires Théa or any of the international regulatory authorities, and no modifications relating to safety information were made to the product label. Laboratoires Théa has received 2 reports of adverse reactions in patients treated with Virgan: one that was not considered to be a serious adverse reaction, but was probably a mild allergy, and one that Laboratoires Théa considered to be misuse of the product since it was prescribed for herpes zoster ophthalmicus, which is not the approved indication (5.3.6; 2.5.5.7).

The Sponsor believes that the results from the clinical safety studies provide evidence to support the benefit-to-risk assessment of ST-605 for the proposed indication of the treatment of acute herpetic keratitis (dendritic and geographic ulcers) and the proposed dosage of 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.

2.5.5.1.1 Safety Endpoints

The safety and tolerance assessments in the clinical studies included AEs; local and systemic tolerance by the investigator and the subject; and hematology, urinalysis, and plasma assays to evaluate possible systemic effects of the drug. Study 6 did not include assessment of local or systemic tolerance by the investigator or the subject, and Study 7 did not include assessments of systemic tolerance.

The sources of AE data included in this summary are from Studies 4, 5, 6, and 7, which were conducted in subjects with acute herpetic keratitis. These studies utilized a CRF with a checklist containing the expected AEs for this disease state, based on previous clinical trials. The CRFs for Studies 6 and 7 also contained a page to report the unexpected AEs. The following were AEs that were treatment-emergent and not due to disease progression:

- Blurred vision
- Eye irritation
- Punctate keratitis
- Conjunctival hyperaemia
- Erythema of the eyelid
- Corneal disorders
- Dacryostenosis acquired

Investigators were instructed to evaluate the AEs, and their presence or absence was captured on the CRF. They were not asked to judge whether the AE was treatment-related, except for punctate keratitis. The severity of the AEs, except for dacryostenosis, was graded on the CRFs using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). Dacryostenosis was graded as 0=no and 1=yes. In addition, in Studies 4 and 5, the investigator and the subject evaluated the local and systemic tolerance of the drugs on a 3-point scale (0=poor, 1=good, 2=excellent). In Study 7, the investigator and the subject evaluated the local tolerance on a 4-point scale (0=bad, 1=poor, 2=good, 3=excellent); the categories of "bad" and "poor" have

been grouped into the single category of "poor" in order to pool the data consistently across studies. Investigator and subject assessments were not performed in Study 6, and assessments for systemic tolerance were not performed for Study 7. The investigators in Study 4 also collected blood samples over time to measure ganciclovir plasma concentration levels, and the investigators in Study 7 collected a 24-hour urine sample to evaluate systemic distribution and clearance of ganciclovir.

Table 1. Phase 1, 2, and 3 Trials Contributing Safety Information for ST-605

Study ID/Protocol No.	Locations	Study Designs	Treatment/Duration	No. of Subjects
Study 1 Protocol No.: 64.GV550/ 04.92	Hôtel-Dieu Hospital, Paris, France	Single-center, open-label	ST-605 or GCV 0.05% 1 drop 5×/day until the ulcer healed, then 3×/day for 7 days (11-15 days)	N=24 ST-605: n=11 GCV 0.05%: n=13
Study 2 Protocol No.: F-94-02	Centre d'Investigation Clinique, Toulouse, France	Single-center, open label	ST-605 1 drop 4×/day for 1 day	N=6
Study 3 Protocol No.: F-94-01	Centre d'Investigation Clinique, Toulouse, France	Single-center, double-masked, randomized, intra-individual (right vs left eye)	ST-605 in 1 eye and vehicle in opposite eye 1 drop in conjunctival sac 5×/day for 7 days	N=10
Study 4 Protocol No.: 42-2.GV550/ 02.90	Mali (Bamako); Senegal (Dakar); Tunisia (Sousse, Tunis)	Comparative, multicenter, randomized	ST-605 or ACV 3% or GCV 0.05% 1 drop 5×/day until the ulcer healed, then 3×/day for 7 days for a maximum of 21 days	N=67 ST-605: n=23 ACV 3%: n=22 GCV 0.05%: n=22
Study 5 Protocol Nos.: 44.GV550/ 12.90 46.GV550/ 07.90	France (Brest, Clermont-Ferrand); Switzerland (Lausanne); United Kingdom (Bristol)	Comparative, multicenter, randomized	ST-605 or ACV 3% 1 drop 5×/day until the ulcer healed, then 3×/day for 7 days for a maximum of 21 days	N=35 ST-605: n=18 ACV 3%:n=17

Table 1. Phase 1, 2, and 3 Trials Contributing Safety Information for ST-605 (continued)

Study ID/Protocol No.	Locations	Study Designs	Treatment/Duration	No. of Subjects
Study 6 Protocol No.: 47.GV550/ 09.90	Pakistan (Karachi)	Comparative, multicenter, randomized, single-masked	ST-605 or ACV 3% or GCV 0.05% 1 drop 5×/day for 10 days	N=109 ST-605: n=36 ACV 3%: n=38 GCV 0.05%: n=35
Study 7 Protocol Nos.: 64.GV550/ 04.92 66.GV550/ 06.92	France (Aulnay-Sous-Bois, Bobigny, Bordeaux [2 sites], Brest, Chambery, Chateaulin, Clermont-Ferrand [5 sites], Cournon, Le Golfe Juan, Lesneven, Marseille, Palaiseau, Paris [2 sites], Thiers, Toulon); Mali (Bamako); Madagascar (Tananarivo); Switzerland (Sousse); United Kingdom (Birmingham, Bristol, Dublin, London)	Comparative, multicenter, randomized, stratified by ulcer type	ST-605 or ACV 3% 1 drop 5×/day until ulcer healed, then 3×/day for 7 days for a maximum of 21 days for dendritic ulcers and 35 days for geographic ulcers	N=164 ST-605: n=84 ACV 3%: n=80

ACV, acyclovir 3%; GCV, ganciclovir

2.5.5.2 Extent of Exposure

A summary of the number of subjects exposed, the treatments received, and the overall extent of exposure across the clinical studies can be found in 5.3.5.3.2, Tables 6.3.1, and 6.3.2. The range of the days of exposure to ST-605 was 0 to 28 days, acyclovir 3% was from 3 to 31 days, and ganciclovir 0.05% was 0 to 21 days. The mean days of exposure was 11.5 days for the ST-605 group, 12.1 days for the acyclovir 3% group, and 9.1 days for the ganciclovir 0.05% group.

2.5.5.3 Adverse Events

Investigators were not asked to judge the relationship of AEs to treatment, except for punctate keratitis. Thus, all AEs in the safety analysis were considered to be treatment related. The intensity of the events was predominantly mild, and the majority of AEs were transient and resolved without sequelae.

Table 2 shows the AEs that occurred across the 4 clinical studies and that will provide the safety information for labeling. AEs for Study 6, other than blurred vision, were collected by the investigators on the CRFs as written comments. This information was not included in the database and, therefore, could not be pooled during the analysis performed by Sirion and is not included in Table 2. Table 3 is a compilation of the written AEs from Study 6 that were collected from the CRFs and the original study reports.

Of the 161 subjects who were treated with ST-605, the most frequently reported ocular AEs were blurred vision upon instillation (57.8%), eye irritation (burning and stinging) upon instillation (25.6%), and punctate keratitis (8.8%) (2.7.4.4.4.1, 2.7.4.4.4.2, 2.7.4.4.4.3). The same AEs were seen in the acyclovir 3% group (N=157), in the same order of frequency, but at a higher incidence: blurred vision upon instillation (71.3%), eye irritation (burning and stinging) upon instillation (46.2%), and punctate keratitis (16%) (2.7.4.4.4.1, 2.7.4.4.4.2, 2.7.4.4.4.3). For the remaining AEs reported, the incidences of conjunctival hyperaemia, erythema of the eyelid, and corneal disorders (other than punctate keratitis) were similar for both groups (2.7.4.4.4.4, 2.7.4.4.4.5, 2.7.4.4.4.6). Dacryostenosis was not reported in any treatment group (2.7.4.4.4.7). Excellent ratings for systemic and local tolerance by the investigators and the subjects were assigned to the ST-605 formulations more often than they were for acyclovir 3% (2.7.4.4.4.9).

There were no SAEs and no deaths reported for the subjects treated with ST-605 in any of the clinical trials. There were only 2 reports of systemic AEs, which was expected because of the very low systemic absorption of ganciclovir into circulation (2.4.3.2). Dysgeusia was reported by a single subject treated with ST-605 as "taste in mouth" in Study 7. There were no withdrawals of subjects due to AEs in Studies 4, 5, and 6 (2.7.4.6.2). In Study 7, 2 subjects treated with ST-605 and 1 subject treated with acyclovir 3% were withdrawn due to AEs (2.5.5.3.2).

The AE data from the three Phase 1 studies were not integrated with the safety data from the 4 clinical efficacy and safety studies. Reasons for not integrating these studies are as follows:

Studies 2 and 3 were conducted with healthy volunteers, who did not meet the inclusion criterion of having an ulcer at baseline in the 4 clinical trials, and therefore, the data could not be pooled. No AEs were reported in Study 2, and 3 AEs were reported in Study 3 (mild conjunctival hyperaemia, few rare follicles, eye irritation upon instillation). Study 1, which was an analysis of blood samples from a subset of the subjects in Study 4, was designed specifically to be a qualitative blood analysis to evaluate the systemic passage of ganciclovir; no AEs were reported for this study.